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## TRAUMATIC INTRACEREBRAL HEMORRHAGE

WITH PARTICULAR REFERENCE TO ITS PATHOGENESIS AND ITS  
RELATION TO "DELAYED TRAUMATIC APOPLEXY"

CYRIL B COURVILLE, M D

AND

OLOV A BLOMQUIST, M D

LOS ANGELES

To those familiar with the effects of trauma on the brain and its envelopes, the importance of the mechanism by which the injury is produced in interpreting the pathologic picture is quite evident. Each type of injury is now known to produce its own characteristic train of lesions. The appalling increase in craniocerebral injuries consequent to traffic accidents has brought into prominence a number of effects which appear to be the direct consequence of striking of a stationary or relatively stationary object by the head in motion. These effects have been long described as *coup-contre-coup* effects. One of the lesions belonging to this group which to date has not been given any selective attention is gross hemorrhage into the cerebral substance—traumatic intracerebral hemorrhage.

In 1891, Bollinger described 4 cases in which death occurred rather suddenly from twelve to fifty days after an injury to the head and proved at autopsy to have been due to hemorrhage into the ventricles or the brain substance. Since that time considerable attention has been given, particularly in the contemporary French and German literature, to a syndrome which has come to be known as "delayed traumatic apoplexy," in the support of which several involved theories have been elaborated. The importance of determining the truth or falsity of this assumption from a medicolegal standpoint, if for no other reason, is clearly evident. Should a patient or his dependents receive compensation or damages as a consequence of an apoplectic stroke which occurs, for example, one month after a cranial injury? Is there evidence to support the assumption that such a condition as delayed traumatic apoplexy actually exists? If so, is there any relation between this condition and gross intracerebral hemorrhage which occurs shortly after an injury to the head?

From the Department of Neurology, College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital

It is the object of this contribution to report our observations in a series of 38 cases of gross hemorrhage into the cerebral substance which followed injury to the head. We propose to discuss the mechanism of production of traumatic intracerebral hemorrhage, to determine its various pathologic types, to present its gross characteristics and to note its ultimate effect on the brain. With the resultant findings to use as criteria, the matter of delayed traumatic apoplexy will then be scrutinized.

#### MATERIAL AND METHODS

For this study the records of a series of 439 cases of fatal cranio-cerebral injury have been studied. In these cases the patient was examined clinically in the neurosurgical service at the Los Angeles County Hospital. The autopsies were performed by the coroner's surgeons, Dr. A. F. Wagner and Dr. John H. Schaefer, who furnished one of us (Courville) with records of their observations and permitted him to make a personal study of the intracranial lesions.

In order to determine the mechanism by which the various lesions were produced, an effort has been made to determine from the hospital notes and other records how the injuries were sustained. Attention was given to the points of application of force to the head as well as to the location of intracerebral injuries. Correlation was also made with the roentgen findings during life and with the location and type of the fracture of the skull observed at autopsy.

In this series of 439 cases, 36 cases of gross hemorrhage into the brain were discovered. Two additional cases were found in the records of the Cajal Laboratory from other sources. We have excluded a number of cases in which the hemorrhages were relatively small, that is, in which the clot was smaller than a cherry. This was done to establish some sort of criterion as to the size of the clot, although even in these excluded cases the mechanism was found to be the same as in the case of the larger hemorrhages. To note any possible effects of injury on the blood vessels or the nerve tissue in the region of the basal ganglions and particularly the internal capsule, the brains in a series of over 80 additional cases of old injury of the brain, sustained between three months and twenty years before death, which resulted from some other cause have also been studied. It is from this list of cases that 2 of the 38 cases of traumatic intracerebral hemorrhage have been taken to show the delayed effects of such hemorrhage.

#### MECHANISM OF CEREBRAL INJURY

In another connection,<sup>1</sup> reference has been made to the mechanism by which traumatic lesions of the brain are produced. Such lesions

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1 Courville, C. B. *Pathology of the Central Nervous System. A Study Based upon a Survey of Lesions Found in a Series of Fifteen Thousand Autopsies*. Mountain View, Calif., Pacific Press Publishing Association, 1937, pp. 181 and 182.

may be the result of a direct or an indirect injury, those due to the former mechanism are most common and of greatest importance. Indirect injury, such as falls on the feet or buttocks or blows to the chin, rarely produce gross cerebral lesions. On the other hand, direct injuries may produce cerebral lesions by (1) compression of the head by some relatively unyielding object, (2) striking of the head by an object in motion and (3) striking of a relatively immobile, solid object by the head in motion. In this last group are to be found injuries sustained in traffic accidents or falls.

In traffic accidents, whether injuries are the result of collision between two automobiles or between an automobile and some relatively stationary object or whether a pedestrian is struck by an automobile, the craniocerebral damage is sustained while the head is in motion. The resultant lesions, namely, certain types of subdural and subarachnoid hemorrhage, contusions of the brain and petechial and gross hemorrhages into the brain substance, are the result of this peculiar mechanism and are designated as *coup-contre-coup* lesions. At the same time, as a result of falls or forcible projection against some relatively immobile object, there may also be sustained direct injuries at the point of impact should the head strike a small object with sufficient force to cause local injuries to the skull.

#### CLASSIFICATION OF TRAUMATIC INTRACEREBRAL HEMORRHAGE

On the basis of the mechanism by which the lesion is produced, a study of our cases disclosed two separate types of traumatic intracerebral hemorrhage. The first type occurs as a consequence of direct injury to the skull and is usually associated with a compound fracture. The second type of hemorrhage is that which is the result of a *coup-contre-coup* mechanism. These hemorrhages in turn may be adjacent consequent to a local contusion, or may occur independently within the cerebral centrum.

*Traumatic Intracerebral Hemorrhage Due to Direct Injury*—It is natural to expect that serious injuries to cerebral or cerebellar vessels by fragments of skull or indriven foreign bodies will be followed by more or less extensive hemorrhage. Whether or not such an injury to the skull is followed by severe bleeding depends entirely on the extent of laceration of the brain and the proximity of the lesion to one of the major arteries or veins. In our experience (with relatively few cases) compound depressed fractures over the area supplied by the middle cerebral artery and its major branches are most apt to be followed by gross hemorrhage.

The immediate effect of an indriven fragment of bone or foreign body is laceration of the brain, the extent of which is naturally limited by the margins of the depressed area and its depth by the extent of



penetration of the fragments from the skull or the associated foreign body. In addition to direct laceration of the brain substance by fragments of the skull, gross effusion of blood into the cerebral substance further results in excavation of a cavity in the brain (fig 1). If the patient survives the injury, the clot absorbs, and a more or less sharply outlined cavity remains directly beneath the defect in the skull. This cavity may extend into the lateral ventricle. It does not present the serious scarring and deformity with adhesion to the dura which accompany a depressed fracture with laceration of the brain without serious hemorrhage.

We have observed but 3 cases which would answer this description, and, interestingly enough, in 2 of them the injuries were old. The essential details of these 3 cases are included in table 1. In the first and

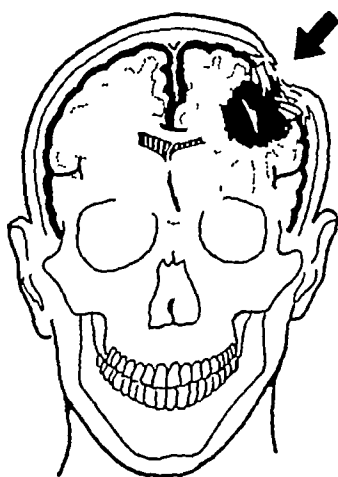


Fig 1—Traumatic intracerebral hemorrhage following direct injury, showing the mechanism of its production. The injury was a compound comminuted depressed fracture with laceration of the cerebral vessels by bone fragments.

TABLE 1—Intracerebral Hemorrhages Consequent to Laceration of the Brain

Case No	Age	Sex	How Injured	Period of Survival	Location of Lesions in Scalp	Injury to Brain	Size and Location of Hemorrhage
1	67	♂	Struck by automobile	61 hours	Left temporo-occipital region	Local depressed fracture of skull with laceration of brain	Recent extensive hemorrhage into left temporal lobe
2	56	♂	Fall from train	18 years	Left parietal region	Local depressed fracture of skull	Old large hemorrhagic cavity in left parietal region
3	57	♂	Gunshot wound	22 years	Left upper central region	Local compound comminuted fracture of skull	Old small hemorrhagic cavity in upper portion of left precentral gyrus

second cases the injury was due to a compound comminuted depressed fracture of the skull. In the second case the lesion was studied some eighteen years after the original injury. The characteristics of this lesion are shown in figure 2. In the third case the brain was examined twenty-two years after an accidental gunshot wound of the head. It presented an irregular cavity in the upper portion of the left precentral gyrus. The details of this lesion have been described in another connection.<sup>2</sup> The old, multilocular cavity was not very extensive, probably the result of indriven fragments of bone as well as of the passage of the bullet. Its fairly smooth walls presented evidence of pigmentation even after this long interval, indicating that a blood clot had occupied this space.



Fig 2 (case 2)—Traumatic porencephaly. Note the old hemorrhagic cavity in the left parietal lobe consequent to compound comminuted depressed fracture of the cranial vault.

*Traumatic Intracerebral Hemorrhage Due to Coup-Contrecoup Injury*—In this larger group of cases cerebral damage was sustained while the head was in motion in the course of an automobile accident or a fall. If the intracerebral hemorrhage in these cases is to be considered actually an effect of the *coup-contrecoup* mechanism, it is necessary that the lesion conform to the rules as far as its location is concerned and it should be comparable in this regard to contusions which are the most typical lesions in this group. A brief statement of the essential factors is here in order.

<sup>2</sup> Courville, C. B. and Kimball, T. S. *Histologic Observations in a Case of an Old Gunshot Wound of the Brain*, Arch. Path. 17:10 (Jan.) 1924.

1 Injury to the frontal region produces a *coup* lesion of the frontal lobes, not infrequently accompanied by a *coup* or *contrecoup* lesion of one or both temporal lobes

2 Injuries to the temporal and parietal regions commonly produce *contrecoup* lesions, less commonly, *coup* lesions of the temporal lobe

3 Injuries to the occipital region produce *contrecoup* lesions of the basilar surfaces of the frontal lobes or of both the frontal and the temporal lobes. Occipital injuries do not produce *coup* lesions

As will be shown, this group of intracerebral hemorrhages fill all the postulates for *coup-contrecoup* lesions, since they were sustained when the head was in motion and were located in parts of the brain which are ordinarily contused by such injuries

#### ANATOMIC CLASSIFICATION

From the study of the cases in our series, we have been able to elaborate the following classification of traumatic intracerebral hemorrhage: (1) hemorrhage into the frontal lobes, which may be either *coup* or *contrecoup*, adjacent or central,<sup>3</sup> (2) hemorrhages into the temporal lobes, which may be *coup* or *contrecoup*, adjacent or central, (3) bilateral cerebral lesions, usually frontal or temporal, indicating both *coup* and *contrecoup* effects, (4) hemorrhage into the ganglionic region which may be either *coup* or *contrecoup* in effect, and (5) hemorrhage into the cerebellum, essentially a *coup* effect

Because of the individual characteristics of the lesions in the various anatomic locations we have chosen to discuss them on this basis

#### TRAUMATIC HEMORRHAGES INTO THE SUBSTANCE OF THE FRONTAL LOBES

Traumatic hemorrhage into the frontal lobes seems to be a fairly common consequence of injury and may be the result of either a *coup* or a *contrecoup* injury. In 13 of our 38 cases the hemorrhage proved to be located in this region. Reference to table 2 discloses some interesting

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3 In this connection it is necessary to define the words "adjacent" and "central," which have been used in the foregoing classification. In this sense, "adjacent" refers to a major hemorrhage directly consequent to a focal contusion of the cortex and subcortex. It is not meant to include, however, the hemorrhage which is an essential part of the contusion itself. In some instances, when the bruise is severe and when some preexisting disease of the blood vessel favors its rupture, a gross effusion of blood into the lobe takes place, which complicates the original lesion and undoubtedly assists in bringing about the patient's death. On the other hand, "central hemorrhages" are those effusions which occur primarily in the centrum of the frontal or the temporal lobe, less commonly elsewhere and often with little or no evidence of focal contusions of the cortex. At times these central hemorrhages extend to and rupture through the cortex, so that this lesion might possibly be mistaken at operation for an "adjacent" hemorrhage.

TABLE 2—*Hemorrhages Into the Frontal Lobes*

Case Sex Age	How Injured	Period of Survival	Location of Lesions in Scalp	Cerebral Contusions	Cerebral Hemorrhages	Conscious Interval
A Coup Hemorrhages						
Adjacent						
4 ♂ 29	Automobile collision	22½ hours	Right and left frontal region	Right and left frontal and temporal lobes	Moderate-sized hemorrhages into right and left frontal lobes	0
5 ♂ 40	Automobile accident	40 hours	Right and left frontal region	Left frontal lobe	Small hemorrhage into left frontal lobe	0
Central						
6 ♀ 43	Automobile collision	13½ days	Right fron tal region	None	Very large hemor rhage into right frontal lobe	2 to 3 hours
7 ♂ 45	Struck by automobile	6¾ hours	Right and left frontal regions	Right and left frontal and right temporal lobes	Small hemorrhage into right and left frontal lobes	0
8 ♂ 72	Struck by automobile	6 days	Right and left frontal regions	Right frontal and temporal lobes	Very large hemor rhage into right frontal lobe	¾ hour
9 ♂ 78	Fall	28 hours	Right and left frontal regions	Right and left frontal lobes	Very large hemor rhage into left frontal lobe	Coma for 2 hours conscious (?) coma
B Contrecoup Hemorrhages *						
Medial Frontal Hemorrhage with Contusions (Typically Adjacent)						
10 ♂ Adult	Automobile accident	50 hours	Occipital	Right and left frontal lobes	Moderate adjacent hemorrhages into left and right frontal lobes	0
11 ♂ 49	Fall (epi lepsy)	16½ hours	Right occip- ital	Right and left frontal lobes	Moderate adjacent left frontal hemorrhage	Complicated by convulsions
Lateral Frontal Hemorrhage Without Contusion (Central with Rupture to Surface [?])						
12 ♂ 44	Fall	7½ days	Left parietal region	Right frontal and temporal lobes	Moderate adjacent hemorrhage into right frontal lobe	Coma few hours con scious 5 days coma 4 days
13 ♂ 62	Fall	4 days	Right occip- ital region	Right and left frontal lobes	Massive adjacent left frontal hemorrhage	0
14 ♂ 37	Struck by automobile	3¼ days	Right occip- ital region	Right and left frontal left temporal lobes	Moderate adjacent left frontal hemorrhage	Incomplete latent interval
15 ♂ 72	Automobile accident	9 days	Left occip- ital region	Right and left frontal lobes	Moderate adjacent right frontal hemorrhage	Incomplete latent interval
Both Adjacent and Atypically Central Hemorrhage						
16 ♂	Struck by automobile	7¾ days	Right and left occip- ital regions	Right and left frontal and right temporal lobes	Numerous moderate adjacent and central hemor rhages into both frontal lobes	Coma for hours conscious 7 days coma 4 days

See discussion in text for classification of this group of cases

points In the first place, it will be noticed that hemorrhage following either *coup* or *contrecoup* injury to the frontal region may be adjacent or central However, as will be shown, these hemorrhages are not so simply classified anatomically The typical adjacent hemorrhages with gross external contusions are usually found within the medial aspects of the frontal lobes There is a second type of hemorrhage, which occurs in the frontal centrum and extends to the surface of the lobe through a

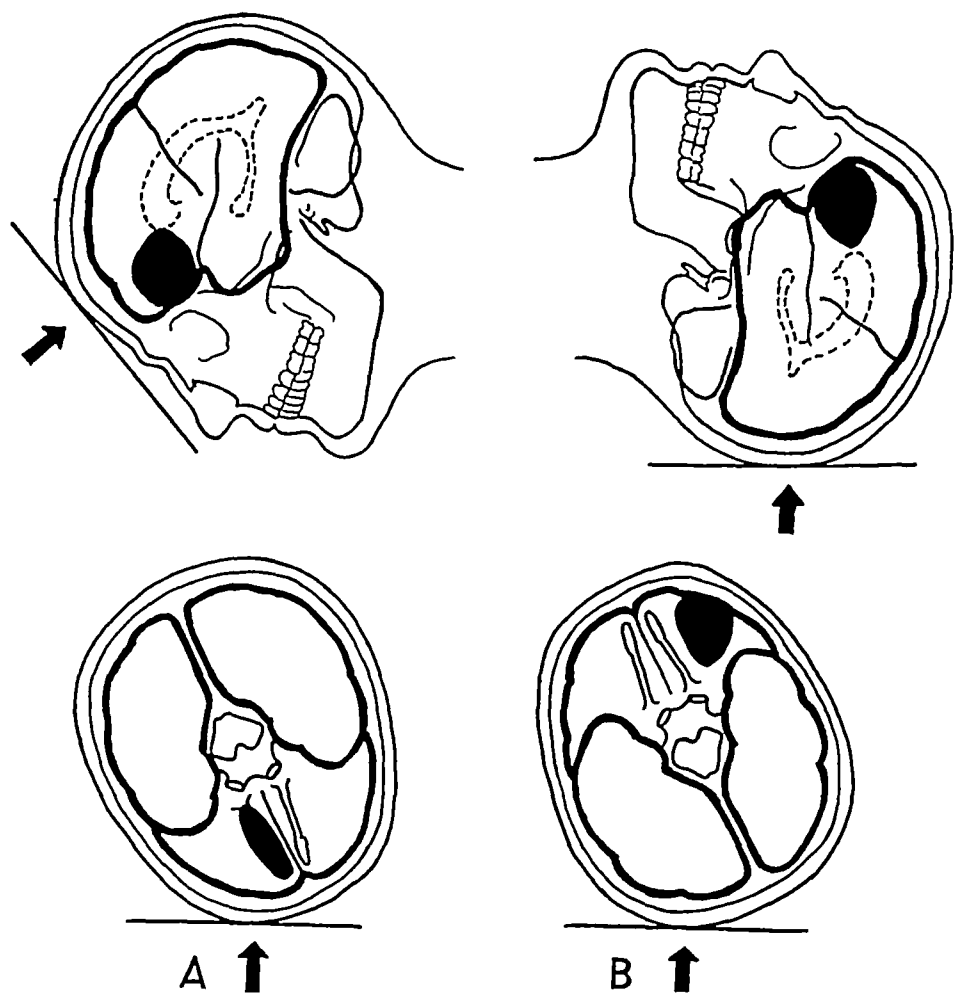


Fig 3—Traumatic hemorrhage into the frontal lobe, showing the mechanisms of its production A, parasagittal hemorrhage from *coup* injury, B, lateral hemorrhage from *contrecoup* injury

semilunar slit along the inferolateral margin of the lobe Whether this is in fact an adjacent or a central hemorrhage will be discussed in the proper section Typical *contrecoup* hemorrhages are rare, being found in only 1 case and then in association with typical bilateral adjacent hemorrhage

*Adjacent Frontal Hemorrhages*—Whether a *coup* or a *contrecoup* effect, according to our definition an adjacent hemorrhage is part of a

focal traumatic lesion of the basilar surface of the frontal lobe. The contusion usually involves the medial aspect of the basilar surface, ordinarily just lateral to the anterior portion of the straight gyrus. From the external contused area, often limited in extent, there extends upward and outward into the brain a narrow hemorrhagic cavity, the anteroposterior extent of which varied considerably in the cases studied. In cases of mild injury it may be a slitlike space in which hemorrhage is seen at autopsy. In other cases this cavity may extend throughout the length of the frontal lobe, rupturing into the anterior horn of the corresponding lateral ventricle with consequent ventricular hemorrhage. In fact, this mechanism constitutes one of the numerous forms of traumatic intra-



Fig. 4 (case 11).—Bilateral traumatic "adjacent" frontal hemorrhages with rupture into the anterior horn of the lateral ventricle (arrow).

ventricular hemorrhage. A fairly characteristic lesion of this sort is shown in figure 2.

*Lateral Frontal Hemorrhage, Possibly Central*.—The second type of intrafrontal hemorrhage, which closely resembles the central type in some respects, is one in which the clot is found more laterally in the lobe. This lesion seems to occur with injuries definitely to one side or the other of the occiput. The hemorrhage is often fairly large and may excavate a considerable cavity in the substance of the homolateral frontal lobe. It extends almost invariably to the surface of the lobe by a slit along the curved inferolateral margin of the frontal lobe. A typical lesion of this variety is shown in figure 3. It may rupture into the anterior horn of the corresponding ventricle. The prolonged period of

survival with the suggestion of a lucid interval clinically and the absence of associated cortical contusion indicate that this lesion is a variety of true central hemorrhage

*Typical Central Hemorrhages of the Frontal Lobe*—Only four typical central hemorrhages occurred as a result of a *coup* injury, and in 3 cases the effusion was large (fig 4) In 1 case of *contrecoup* injury several paracentral hemorrhages were observed in association with adjacent hemorrhages Central hemorrhages in *coup* lesions are frequently accompanied by a more or less definite contusion of the subfrontal region and are therefore indicative of a rather severe injury to the head

In spite of this, it is of interest to note that there is a rather long period of survival, suggesting a progressive lesion in such cases Attention should be called to 1 case in particular (case 6, table 2) A patient survived for thirteen and one-fourth days after an injury to the head in which the essential lesion was a massive hemorrhage into the right frontal lobe Since there was a period of consciousness following the accident, it seems quite likely that the hemorrhage, evidently initiated in some way by the injury, continued until death ensued In this sense the lesion is characteristic of a delayed traumatic hemorrhage More attention will be drawn later to this question of delay in onset of the symptoms provoked by the hemorrhage

As for the *contrecoup* type of hemorrhage, although it is adjacent in every case, the rather prolonged period of survival is a matter of special interest The patient survived a number of days in all but 2 cases It should also be noticed that in this group of cases there occurred in a number of instances what appeared to be an interval of consciousness after transitory short periods of coma, with a subsequent relapse into coma and eventual death

#### TRAUMATIC HEMORRHAGES INTO THE TEMPORAL LOBE

From a study of table 3 it will be found that *coup* hemorrhages of the temporal lobe, either adjacent or central, were rather rare This is in accord with the relative infrequency of contusions of the temporal lobe on the same side as the injury *Contrecoup* lesions of the temporal lobe are the rule It will furthermore be observed that in the larger group of *contrecoup* hemorrhages, most effusions occur in the centrum of the lobe They are not accompanied with local contusions, although at times *coup* contusions of the frontal lobe may be present This leads one to conclude that, although temporal contusions may be so severe as to provoke a local hemorrhage, central hemorrhages are more apt to occur as a *contrecoup* effect of the injury Furthermore, these central effusions into the central lobe are frequently large and in this regard would correspond closely to spontaneous hemorrhages into the brain

TABLE 3—*Hemorrhages Into the Temporal Lobe*

Case Sex Age	How Injured	Period of Survival	Location of Lesions in Scalp	Cerebral Contusions	Cerebral Hemorrhages	Conscious Interval
A Coup Hemorrhages						
Central						
17 ♂ 23	Motorcycle accident	3½ days	Right frontal and temporal region	None	Small central hemor- rhage into right temporal lobe	0
18 ♀ 50	Automobile accident	17½ hours	Left tem- poral region	Left and right frontal and right temporal lobes	Large central hemor- rhage into left temporal lobe	0
B Contrecoup Hemorrhages						
Adjacent						
19 ♂ 35	Fall	15 hours	Left tem- poral region	Right and left temporal lobes	Large adjacent hemorrhage into right temporal lobe	0
20 ♂ 35	Fall from horse	61 hours	Left temporo- parietal region	Right temporal lobes	Massive adjacent hemorrhage into right temporal lobe with con- sequent subdural hemorrhage	No prelimi- nary coma after 18 hours
21 ♂ 40	Struck by automobile	18 hours	Left frontal region	Right temporo- occipital region	Moderate adjacent hemorrhage into right temporo- occipital region	0
Central						
22 ♂ 57	Fall	10 days	Right tem- poral region	None	Massive central hemorrhage into left temporal lobe	89 day interval
23 ♂ 70	Struck by automobile	3 days	Right fron- tal region	None	Multiple small central hemor- rhages into left temporal lobe	Suggestive interval
24 ♂ 75	Struck by automobile	32 hours	Right fronto- temporal region	None	Massive central hemorrhage into left temporal lobe	0
25 ♂ 35	Fall	4½ days	Right tem- poral region	None	Massive central hemorrhage into left temporal lobe	No interval survival period pro- longed by operation
26 ♂ 55	Struck by motorcycle	8½ days	Right fronto- temporal region	Right frontal and temporal lobes	Massive central hemorrhages into left temporal lobe	Preliminary coma then partial recovery followed by coma
27 ♂ 2	Fall	4 days	Right tem- poral region	None	Massive central hemorrhage into left temporal lobe	Interval 1½ hours
28 ♂ 45	Fall	About 6 days	Right fron- tal region	Left temporal lobe	Massive hemor- rhage into left temporal lobe	Interval *
29 ♂ 45	Automobile accident	7 months	?	None	Old hemorrhagic cavity with exten- sion to basilar surface of temporal lobe and lateral ventricle	*



Particular emphasis should be placed on this point, because it is this group of cases in which the hemorrhage is severe enough to require serious clinical consideration, demanding therapeutic attention in and of itself. This differs from adjacent intracerebral hemorrhage, which is a part of an already serious and extensive lesion. Moreover, the patients frequently have a prolonged period of survival, at times with a lucid interval, or symptoms may come on gradually and progressively after a relatively minor frontal injury. This also suggests the likelihood that such hemorrhages are progressive lesions, initiated in some way by the injury and producing symptoms by a gradual accumulation of blood in the centrum. A deepening coma ultimately results in the patient's death.

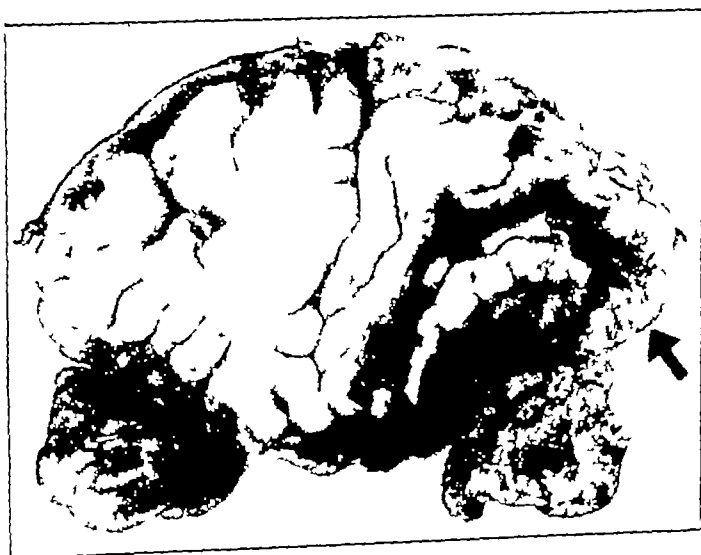


Fig 5 (case 13) —“Central” traumatic frontal hemorrhage with rupture to the surface (arrow) along the inferolateral margin of the lobe

*Adjacent Hemorrhages into the Temporal Lobe*—Adjacent hemorrhages of the temporal lobe correspond to those of the frontal lobe and evidently have a similar mechanism. A severe temporal contusion is accompanied by a laceration of the cortex and subcortex. This laceration extends into the brain, tearing some of the regional vessels, with consequent hemorrhage. When the effusion is of sufficient size, a cavity is excavated in the white matter of the temporal lobe, at times followed by rupture into the interior horn of the lateral ventricle, another cause of traumatic intraventricular hemorrhage. Usually this hemorrhage is small, but if a large vessel is lacerated or some preexisting vascular disease predisposed to a more extensive effusion the entire central portion of the lobe may be excavated (fig 5). Such hemorrhage adds to the edema provoked by the original contusion and no doubt contributes much to the fatal issue in these cases. These hemorrhages likewise

give rise to definite lateralizing phenomena, which encourage the surgeon to do a decompression in the hope of finding a subdural clot. At operation the clot may rupture spontaneously through the exposed cortex into the field of the decompression, or it may be discovered by needling the temporal lobe. Indeed, with a basilar contusion it may be difficult for the surgeon to determine whether he is dealing with a primary central hemorrhage or an adjacent one.

*Central Hemorrhages of the Temporal Lobe*—As will be seen by referring to table 3, gross hemorrhages into the temporal or temporo-occipital region may be either a *coup* or a *contrecoup* effect, usually the latter. The resulting lesion seems to be characteristic in that there is



Fig 6 (case 8)—Unusual type of "central" traumatic hemorrhage into the frontal lobe with rupture into the body of the right lateral ventricle (arrow). A small "adjacent" hemorrhage into the ipsilateral temporal lobe is also shown.

a massive effusion of blood into the temporal or temporo-occipital centrum without local cortical contusions. This is an area rarely involved by spontaneous hemorrhage. These hemorrhages are often extensive (fig 6), although in 2 cases in our series the hemorrhages were small.

Although they are obviously *contrecoup* lesions, central hemorrhages into the temporal lobe are relatively infrequent. This may be explained by some by the fact that hemorrhage does not occur unless the injury is severe. On the other hand, the absence of superficial contusion in such cases seems to make this supposition rather untenable. Arteriosclerosis may play an important role, for a considerable number of the patients are beyond middle life. On the other hand, in several instances in this study the patient was relatively young (23 years of

age in 1 case) The influence of other vascular diseases, such as syphilis, seems to be negligible, although the possibility of hypoplasia of the arteries, which predisposes to easy rupture by trauma, may account for this particular phenomenon These facts make it seem very likely that either some peculiar mechanism of the injury itself or, more probably, some other predisposing factor accounts for its occurrence

These effusions excavate an elongated fusiform cavity in the temporal and adjacent occipital centrum, conforming to some extent to the radiation of white fibers in these lobes The occurrence of a lucid interval after a preliminary period of unconsciousness suggests that the hemorrhage is a progressive one, increasing in size as the hours and days pass The longest period of survival in this series was ten days In this respect the lesion qualifies as delayed traumatic apoplexy The

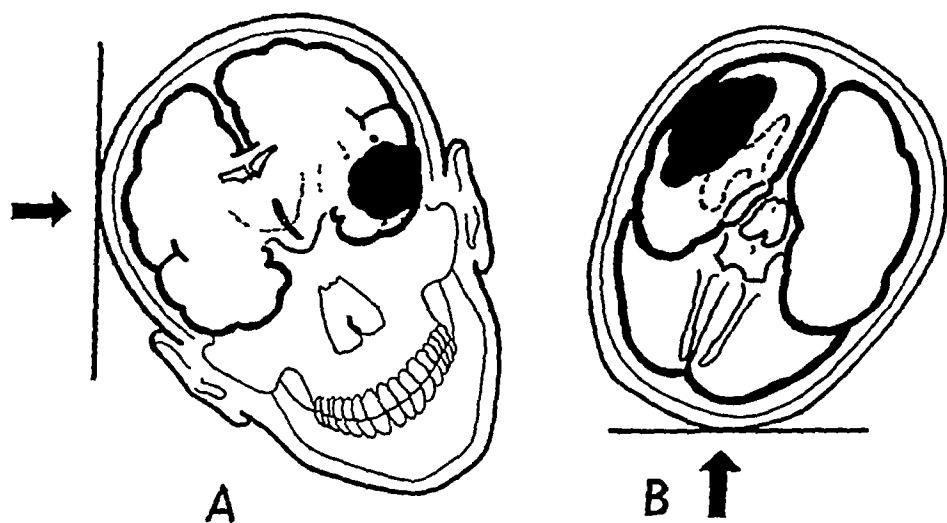


Fig 7—Traumatic hemorrhage into the temporal lobe, showing the mechanism of its production A, *contrecoup* "adjacent" hemorrhage, a part of a gross contusion of the lobe, B, *contrecoup* "central" hemorrhage

mechanism of progressive bleeding scarcely accounts for those cases in which weeks or even months elapse between the time of injury of the vessel and death The evolutionary character of the lesion is strongly indicated by the progressive clinical course when the patient survives for several days

It is a fairly common thing for these large effusions to rupture through the cortex or into a ventricle There seems to be no particularly specific location where this rupture takes place At times it occurs well forward in the temporal lobe, often through the superior temporal gyrus or sulcus More commonly, however, it occurs lower on the dorsolateral surface, through the middle or inferior gyri or sulci, well toward the posterior portion of the lobe Not infrequently, however, the effusion ruptures through the basilar surface of the lobe The overlying leptomeninges are torn, and there is a gross effusion of blood into the subdural

space In such cases the findings at operation may lead to the belief that the subdural hemorrhage is primary, the surgeon not being able to discover its exact source Not infrequently the effusion breaks through into the lateral ventricle (fig 7) In the great majority of cases a massive hemorrhage into the temporal lobe results fatally unless by chance the cavity is surgically excavated either directly through the cortex or by draining the effusion in the subdural space after its rupture Evacuation of the subdural clot, however, is often incomplete and ineffectual, and death occurs

#### HEMORRHAGES INTO BOTH FRONTAL AND TEMPORAL LOBES

As will be noted in table 4, hemorrhages into both the frontal and the temporal lobes are relatively infrequent In certain severe injuries

TABLE 4—*Hemorrhages Into the Frontal and Temporal Lobes*

Case No	Age	Sex	How Injured	Period of Survival	Location of Lesions in Scalp	Injury to Brain	Size and Location of Hemorrhage
A Coup Hemorrhage							
30	35	♂	Struck by automobile	12 hours	Right and left frontal region	Right and left frontal and temporal lobes	Adjacent hemorrhages in right frontal and left temporal lobes
B Contrecoup Hemorrhage							
31	79	♂	Fall	42 hours	Right occipital region	Left frontal lobe	Adjacent hemorrhage in left frontal and central hemorrhage in left temporal lobe

both the temporal and the frontal lobes are injured, and (rarely) hemorrhages into the contusions in both these locations may contain gross blood clots with extension into the centrum This is probably a matter of coincidence in severely injured patients and has no clinical significance It will be noted that in most of the cases the hemorrhages were "adjacent" except in the second case, in which the lesion was "central"

#### BILATERAL HEMORRHAGES INDICATING BOTH COUP AND CONTRECoup EFFECTS

In table 5 the essential findings in a series of 4 cases are recorded in which hemorrhages were observed in both cerebral hemispheres occurring as a rule in a line which points out the line of force produced by trauma This through and through effect is manifested by hemorrhages extending through the centrum of the brain An exception is noted in case 33 in which there were observed hemorrhages secondary to contusions of both temporal lobes a rather unusual situation These

effusions were small, the largest apparently located on the side of a trauma. A rather interesting situation is found in the first case in this series, in which hemorrhages were observed in both external capsules and the left lenticular nucleus. In the following section further attention will be drawn to the question of hemorrhages in the ganglionic region.

This series of cases is probably of no special clinical significance, those patients who survived for a few hours having been so seriously hurt that the intracerebral hemorrhages were simply a part of the general pathologic picture. Perhaps of greater importance in these cases is the suggestion of the true *coup-contra-coup* mechanism. Attention has already

TABLE 5—*Bilateral Hemorrhages Indicating Both Coup and Contre-coup Effect*

Case, Sex, Age	How Injured	Period of Survival	Location of Lesion in Scalp	Injury to Brain	Size and Location of Hemorrhage	Conscious Interval
32 ♂ 70	Automobile accident	3 hours	Left tem- poral region	Right temporal lobe	Multiple small to moderate central hemorrhages in left and right external capsules and left lenticular nucleus	0
33 ♀ 50	Struck by automobile	5½ days	Left temporo- occipital region	None	Multiple small to moderate central hemorrhages into right temporal and left temporo- occipital regions	0
34 ♀ 66	Automobile collision	18½ hours	Left tem- poral region	Right and left temporal lobes	Moderate left and small right adjacent hemorrhages in temporal lobes	0
35 ♂ 80	Fall	29½ hours	Right occip- ital region	Left frontal and temporal lobes	Multiple moderate and central hemorrhages into left frontal and temporal lobes and small hemorrhage into right temporo- occipital centrum	0

been drawn by one of us (Courville) to certain cases in which a line of lesions through the brain is seen at autopsy. This suggests that the line of force extends directly through the brain across the diameter of the skull, indicating that the *contre-coup* lesion is probably a result of direct transmission of force rather than of any of the peculiar mechanisms which have been suggested. The string of lesions in this series of cases strongly indicates that this is the case. Why this occurs in a relatively few cases and why the ganglionic region is apt to be spared it is difficult to determine. The central, or ganglionic, part of the brain, lying as it does beneath the inferior margin of the falx, may be more easily displaced from side to side without causing serious injury in this location.

## HEMORRHAGES IN THE GANGLIONIC REGION

In table 6 is recorded a series of cases in which small hemorrhages were observed in the lenticular nucleus, commonly the putamen, or extending into the *external* capsule. In half of these cases the hemorrhages were also seen in other locations and have already been included in other groups. In the remaining 3 cases the hemorrhages were limited

TABLE 6—Traumatic Hemorrhages Into the Ganglionic Region (*External Capsule and Lenticular Nucleus*)

Case S x Age	How Injured	Period of Survival	Location of Lesion of Scalp	Injury to Brain	Size and Location of Hemorrhage	Conscious Interval
7* ♂ 32	Struck by automobile	7½ days	Occipital region	Right and left frontal and right temporal lobes	Multiple moderate adjacent and central right and left frontal hem- orrhages clot about size of marble in right lenticular nucleus	Coma few hours then conscious three days terminal coma four days
36 ♂ 62	Struck by automobile	7 days	Left tem- poral region	None	Small hemor- rhages left lentle- ular nucleus large hemorrhage right external capsule	Persistent coma
37 ♂ 62	Automobile collision	3¼ days	Left tem- poral region	Right tem- poral lobe	Small hemorrhage into right exter- nal capsule	0
38 ♀ 6	Fall	4½ hours	Right fronto- temporal region	None	Moderate hemorrhage into left external capsule	0
2 ♂ 40	Automobile accident	40 hours	Right and left frontal regions	Left frontal lobe	Small adjacent hem- orrhage in left frontal lobe marble sized clot in left lenticular nucleus	0
27* ♂ 70	Automobile accident	8 hours	Left tem- poral region	Right tem- poral lobe	Multiple small to moderate hemorrhages in left and right external capsules and left lenticular nucleus	0
4 ♂ 15	Automobile accident	2½ hours	Right and left frontal regions	Right and left frontal and temporal lobes	Marble sized clot into right lentle- ular nucleus	0

\* It will be noted that there is some duplication in this table some of the cases being found also in previous groups

to the external capsule or the lenticular nucleus (fig 8). These hemorrhages too may be manifestations of either *coup* or *contrecoup* injury, that is, they may occur on the same side as the external injury or on the opposite side. Of particular interest in this group are those cases in which an injury to the frontal or the occipital region results in a small focal hemorrhage in the lenticular nucleus of the same or the opposite side. Such an injury is probably a modification of the "through and through type" of trauma, as is suggested by some of the cases in the group. Since the occipital lobe is unaffected by either *coup* or

*contrecoup* lesions, the absence of hemorrhages in this lobe tends to impair the otherwise complete impression of through and through injury in these cases. Attention will be again drawn in a later section to this matter of hemorrhages in the ganglionic region.

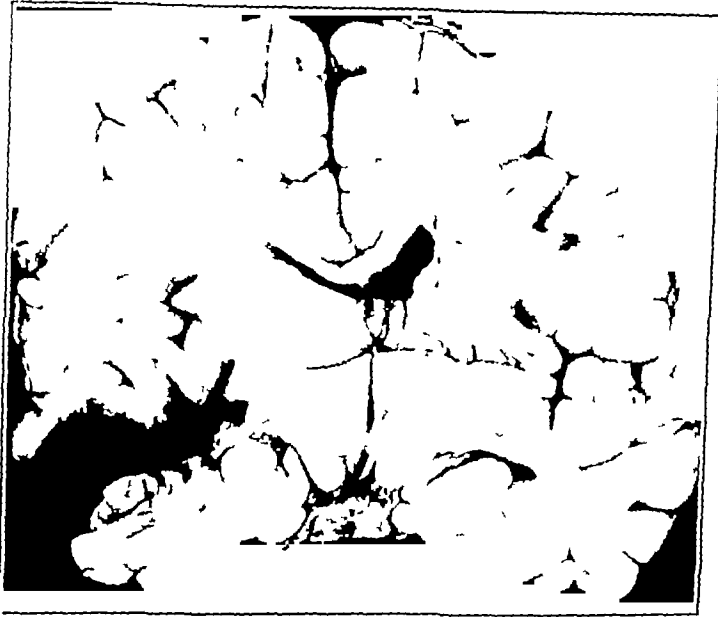


Fig 8 (case 20) —“Adjacent” traumatic hemorrhage into the temporal lobe. The consequent edema and distortion of the ventricular pattern are also shown.

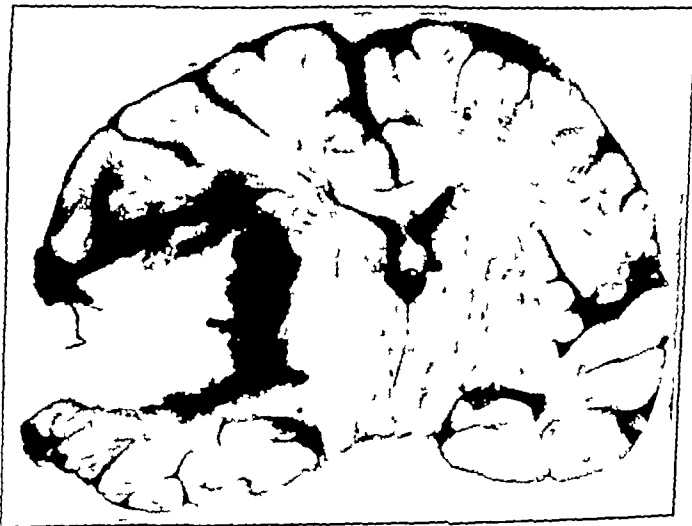


Fig 9 (case 25) —“Central” traumatic hemorrhage into the temporal lobe. The unusual size of the cavity and the place of rupture to the surface as well as consequent edema and distortion of the ventricular pattern are shown.

#### COMMENT

It will be seen from a study of this series of cases that intracerebral hemorrhages are essentially a *coup-contrecoup* effect, the injury being



Fig 10 (case 26) —Massive “central” traumatic hemorrhage *contracoup* into the temporal lobe with rupture into the lateral ventricle as well as to the surface (arrows) A *coup* hemorrhage of the frontal lobe is also shown The broken line shows the direction of force.

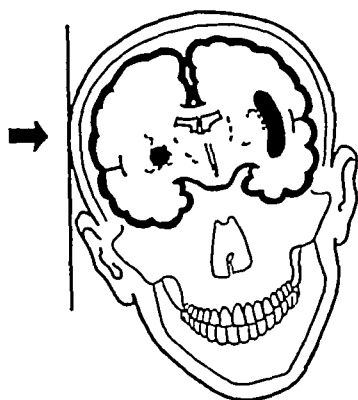


Fig 11 —Traumatic hemorrhage into the ganglionic region showing the mechanism of production The *coup* hemorrhage occurred into the lenticular nucleus and the *contracoup* hemorrhage into the external capsule



sustained with the head in motion. An exception to this rule is the relatively rare occurrence of hemorrhage into the brain following compound comminuted depressed fractures with laceration of the brain by undriven fragments of bone or foreign bodies or probably still more rare instances of penetrating wounds of the skull by a bullet or an edged weapon.

The large group of *coup-contre-coup* hemorrhages may be divided into two subgroups—*adjacent* or *secondary* ones, which are a part of a severe contusion, and *central*, or *primary*, ones in which hemorrhages occur primarily in the centrum of the lobe. Adjacent hemorrhages are to be grouped with the contusion of which they are an essential part, and the severity of the hemorrhage in these cases is dependent largely on the force of the original injury and the friability of the vessels in a given



Fig. 12 (case 32) —Traumatic hemorrhages into the right external capsule and the left lenticular nucleus. The hemorrhage on the right has broken into the lateral ventricle (arrow). The line of force is indicated by the interrupted line.

brain. From the standpoint of traumatic apoplexy, no further attention need be given this group of adjacent or secondary hemorrhages.

Of the group of central, or primary post-traumatic, cerebral hemorrhages there is more to be said. It has been definitely shown that this group of hemorrhages, like the adjacent ones, are a manifestation of the *coup-contre-coup* mechanism, particularly *contre-coup*. At times these hemorrhages are small. On other occasions they are sufficiently extensive to assume clinical importance. This is particularly true of those which occur in the frontal or the temporo-occipital region and which at times seem to follow a relatively minor injury. In these instances, after a latent interval, a progressively increased intracranial pressure results in coma. In this respect, a large central hemorrhage produces a clinical picture which resembles more or less closely that of dural hemorrhage.

with a lucid interval, with which it may be easily confused clinically. This interval was prolonged in 1 of our cases as long as eight to nine days, death occurring on the tenth day after the original minor injury.

There is probably some factor other than the *contrecoup* mechanism in these cases. Otherwise it would be relatively much more common, comparable perhaps in frequency to the cortical contusion, which is found in approximately two thirds of patients coming to autopsy after injury of the head. One possible reason for this is that the lesion is a deeper one and that therefore the part affected is less apt to be traumatized as a result of the force of the blow. The force transmitted through the brain is more widely diffused in these distant parts, which is not so easily possible in the closely invested frontal fossae.

Since a number of these hemorrhages occurred in patients beyond middle age, the possibility of arteriosclerosis or other vascular disease must also be considered. It is logical to believe that atherosclerosis may predispose to rupture of a vessel which would otherwise be unaffected in a younger patient. On the other hand, it must be admitted that a fair number of hemorrhages have occurred in young adult patients in whom no arteriosclerosis was present. Whether or not hypoplasia of the cerebral arteries, which is observed in some instances, is a cause of hemorrhage cannot now be determined with certainty. One of us (Courville) has observed that hypoplasia of the cerebral vessels does play an important part in some cases in which gross effusions of blood on the basis of relatively minor injuries have taken place. On the other hand, whether this phenomenon can be invoked to account for all central hemorrhages in younger persons is only a matter of conjecture. Further study must be given this point before a final answer can be made.

#### "DELAYED TRAUMATIC APOPLEXY"

Much has been said in the literature about "delayed traumatic apoplexy," a term now almost half a century old. The designation carries with it the idea of gross hemorrhage into the brain occurring some time after an injury to the head. The question has important connotations from a medicolegal standpoint and is therefore an important one to settle one way or the other. Since, in this study, the basis has been laid for an understanding of the mechanism and morbid anatomy of traumatic intracerebral hemorrhage, it seems advisable to take the next step and determine, if possible, whether traumatic hemorrhage into the brain can be delayed and how long, what its predisposing lesions may be and how this supposed entity differs, if it does differ, from hemorrhage as a consequence of arteriosclerosis with or without hypertension.

The history of this interesting question of delayed post-traumatic apoplexy has been divided by Duret<sup>4</sup> into four periods, which bring the investigator up to the time of publication of Duret's monograph on craniocerebral injuries in 1922. The first period begins with the introduction of the concept by Bollinger<sup>5</sup> in 1891, who reported a series of 4 cases in which the patients died suddenly with an apoplectic hemorrhage after a period of lucidity varying from twelve to fifty days after injury to the head. In 3 of these cases a blood clot was found in the fourth ventricle, and in the fourth a hematoma was found in the white substance of the centrum ovale, adjacent to the lateral ventricle. Bollinger expressed the belief that these hemorrhages occurred in an area of softening provoked by the cranial shock. In the next six or seven years a number of cases were reported which seemed to confirm this opinion. In 1 in particular, the case reported by Michel,<sup>6</sup> the patient died eight days after injury. At autopsy a hemorrhage about the size of an egg was found in the right occipital lobe, which had ruptured into the occipital horn of the ventricle. This hemorrhage was evidently the result of a *contrecoup* lesion, the patient having sustained an injury to the frontal region.

During the second period, certain objections to the theory were raised by some observers, who questioned whether such hemorrhages are truly traumatic. Langerhans,<sup>7</sup> in particular, expressed the opinion that the hemorrhage is incident to some predisposed vascular condition, such as hypoplasia, anemia or arteriosclerosis, the diseased vessel being ruptured by the shock of trauma.

In 1904 Bailey<sup>8</sup> recognized three varieties of traumatic hemorrhage. He stated that the first type occurs at the moment of injury, the rupture of the vessel being due to the immediate force of the injury or to the increased arterial hypertension provoked by it. In the second type, vascular rupture is produced a little time after the injury, the exact mechanism of which was not possible to determine. In the third type, apoplectiform symptoms appeared a considerable time after injury, apparently due to thrombosis in the region of the brain traumatized by the accident.

4 Duret, H. Traumatismes crâniocérébraux. Accidents primitifs, leurs grandes syndromes, Paris, Felix Alcan, 1922, vol 3, pt 2, pp 833-851.

5 Bollinger, O. Ueber traumatische Spätapoplexie, ein Beitrag zur Lehre von der Hirnerschütterung, in Internationale Beiträge zur wissenschaftlichen Medizin, Festschrift, Rudolf Virchow gewidmet zur Vollendung seines 70. Lebensjahres, Berlin, A. Hirschwald, 1891, vol 2, pp 457-470.

6 Michel, E. Ein Beitrag zur Frage von der sogenannten traumatischen Spätapoplexie, Wien klin Wchnschr 9 789-793, 1896.

7 Langerhans, R. Die traumatische Spätapoplexie, Berlin, A. Hirschwald 1903.

8 Bailey, P. Traumatic Apoplexy, M Rec 66 528 1904.

During this period Lafforgue<sup>9</sup> introduced the conception that delayed cerebral hemorrhage is due to an earlier hemorrhage, or in other words, a hemorrhage occurring in two stages

In 1905 Lambert<sup>10</sup> concluded that in certain cases of traumatic hemorrhage occurring either early or late, the arteries have been structurally altered by preexisting disease constituting a *locus minoris resistentiae*. The diseases which, according to him, predispose to rupture of the vessels are alcoholism, gout, arteriosclerosis and syphilis

In the third period, investigators were concerned largely with the discussion of certain types of hemorrhages, particularly those in the pontobulbar region or in the meninges which occurred at varying intervals after injury to the head. These lesions consisted of local collections of old blood in the pons or in the subarachnoid space which gave rise to symptoms several weeks or even months after the injury

In the fourth period, primary traumatic intracerebral hemorrhages little or large, were recognized as being possible after injury and some extended the conception to include intraventricular and pontobulbar hemorrhages. The microscopic investigations of von Holder<sup>11</sup> led him to conclude that delayed hemorrhages are the result of multiple small lesions affecting the walls of the blood vessels, consisting of small tears and consequent dilatations of local capillaries, in other words, that they are small aneurysms with focal hemorrhages within the perivascular sheath or in its immediate vicinity. Hanzer<sup>12</sup> subsequently described the existence of small areas of softening in the nervous centers along the tract of the axis of percussion. It was then concluded that these small microscopic lesions which followed injury, although silent for some time ultimately permitted a gross hemorrhagic effusion in this vicinity through a rupture in the wall of the vessel

To bring the subject up to date it must be said that, although certain basic truths have become evident in the passing years, there is still much confusion and uncertainty about the whole question. In 1926, Beitzke<sup>13</sup> drew certain conclusions which are in full accord with our observations. He stated (1) that traumatic intracerebral hemorrhage is always at the periphery of the brain and either directly beneath the point of injury or on the opposite side (*coup-contre-coup*) and (2) that if the hemorrhage

9 Lafforgue, E. Hemorragies intra-craniennes traumatiques évoluant en deux temps. *Bull. med.*, Paris 18 875-878, 1904

10 Lambert, P. Hemorragies cerebrales tardives d'origine traumatique traumatische Spätapoplexie, Thesis, Paris, no 411, 1906

11 von Hölder, H. Pathologische Anatomie der Gehirnerschütterung beim Menschen. Stuttgart, J. Weise, 1904

12 Hanzer, cited by Duret<sup>4</sup>

13 Beitzke, H. Pathologisch-anatomisch Diagnostik an der Leiche nebst Anleitung zum Sezieren, Munich, J. F. Bergmann 1926

has taken place only after weeks there is the greatest doubt whether it is actually due to the injury Kaufmann<sup>14</sup> emphasized the point that it is rare to find a traumatic hemorrhage in the basal ganglions, where spontaneous hemorrhages are so frequent

In 1928, Naftziger and Jones<sup>15</sup> reported 3 cases of "late traumatic apoplexy" In 2 of the 3 the mechanism of injury was force applied directly to the head, the hemorrhages being in the temporal lobe beneath the point of injury Since in our series the hemorrhage was sustained when the head was in motion, it is difficult to account for these lesions unless perchance some preexisting vascular lesion predisposed to rupture by local injury

Undoubtedly cases will arise in which the mechanism is not clear A case in point is that reported by Rosenhagen,<sup>16</sup> in which a right precentral subcortical hemorrhage was found about five weeks after a direct injury to the right frontoparietal region Unfortunately, in many of these uncertain cases, other possible causes of hemorrhage are not sought and eliminated

The most conclusive recent article seems to be that of Eck<sup>17</sup> He cited Singer,<sup>18</sup> who laid down certain postulates or criteria by which cases of presumed traumatic hemorrhages are to be judged These postulates are as follows 1 The injury to the head must be severe enough to cause definite injury to the intracranial content 2 The vascular system must be sound before the injury 3 Evidences of commotio cerebri and its consequences must lead directly to the apoplectic stroke 4 Clinical objective signs of changes in the brain must be perfectly evident 5 The interval between the development of the hemorrhage and the injury should not be less than one day or greater than eight weeks Eck reported a case in which the condition seemed to answer to the description of a true post-traumatic intracerebral hemorrhage The case reported by Bettinger<sup>19</sup> likewise seems to be a classic example

14 Kaufmann, E Pathology for Students and Practitioners, translated by S P Reiman, Philadelphia, P Blakiston's Son & Co, 1929, vol 3, p 1890

15 Naftziger, H C, and Jones, O W, Jr Late Traumatic Apoplexy Report of Three Cases with Operative Recovery, California & West Med. 29:361-364, 1928

16 Rosenhagen, H Ueber postkommotionelle Veränderungen im Gehirn, zugleich ein Beitrag zur Frage der posttraumatischen Hirnblutungen, Klin Wchnschr 9 601-604, 1930

17 Eck, H Beitrag zur Lehre der traumatischen Spätapoplexie, Virchows Arch f path Anat 284 67-83, 1932

18 Singer, K Die sogenannte traumatische Spätapoplexie, Ztschr f d ges Neurol u Psychiat 75 127-137, 1922

19 Bettinger, H Ueber traumatische Hirnblutung, Ztschr f d ges Neurol u Psychiat 148 570-573, 1933

In summarizing the period since the appearance of Duret's discussion of the question, it seems evident that in many of the reported cases of delayed traumatic apoplexy the diagnosis was based on clinical evidence alone and is not to be relied on, in others, the hemorrhages were obviously spontaneous effusions into the basal ganglions, the previous trauma being merely incidental, and in still others trauma was probably contributory, with some underlying vascular disease or anomaly at fault. In many instances no serious attempt was made to eliminate other factors, and the case was reported as "delayed traumatic apoplexy."

In conclusion, a study of the literature indicates that these alleged delayed post-traumatic hemorrhages occur not only in the centrum but in or about the ventricles and in the pons as well. The three theories which have been utilized to account for the phenomenon are (1) the theory of necrotic softening, (2) the theory of preexisting alterations in the blood vessel wall and (3) the theory of recurrent hemorrhage. As for the first theory, it is believed that trauma results in the formation of multiple foci of softening in the brain, particularly in the immediate vicinity of the ventricular walls and in certain regions of the white matter, these foci resembling contusions of the cortex and subcortex. In the second theory it is predicated that the injury directly or indirectly produces changes in the wall of the blood vessels in the form of focal aneurysms, which were in turn predisposed to by arteriosclerosis, syphilis, alcoholism or Bright's disease. Secondary alterations are presumed to be due to a transitory physiologic or accidental arterial hypertension which traumatism exaggerated or favored by congestion of the centers of the brain. The third theory of delayed hemorrhage postulates a small primary hemorrhage in the region of the blood vessel as the direct result of the injury. As these initial lesions clear away, there remains a small residual aneurysm, a focal area of softening or regions of capillary apoplexy which permit the subsequent development of gross effusion of blood into the brain.

Just how well all this discussion of delayed traumatic apoplexy fits the basic principles brought out by a study of unequivocal post-traumatic cerebral hemorrhages remains to be told.

#### RELATION OF RECENT TO DELAYED POST-TRAUMATIC HEMORRHAGES

From our study of well defined and unmistakable hemorrhages into the cerebral centrum following injury, certain deductions may be drawn which should be useful in evaluating the problem of delayed post-traumatic hemorrhage.

As a result of our investigation it seems quite clear that symptoms of a hemorrhage may occur within a certain interval after trauma. Aside

from those due to direct laceration of the brain, these hemorrhages are essentially *coup-contrecoup* lesions. Although it is not definitely proved, it seems very likely that injuries resulting from a direct blow to the head at rest will not cause a hemorrhage within the brain substance unless there is some serious disease of the blood vessels. Furthermore, it seems obvious that the delayed post-traumatic hemorrhages in some of the reported cases bear some relation in time of occurrence and location to those which have been shown to be of traumatic origin. Such hemorrhages are to be expected in the centrum of the frontal or temporo-occipital region rather than in the posterior limb of the internal capsule, in the ventricles or in the brain stem as some have supposed. One of us (Courville) has observed that traumatic ventricular hemorrhages have usually proved to be secondary to extensive and massive hemorrhages within the centrum and are not primary in the sense of having their origin in paraventricular lesions.

The one question which has not been entirely established by our studies is that of the interval between the injury and the onset of clinical symptoms. In all of our cases in which the patients did not die within a day or two because of the severity of the injury the earliest symptoms came on within two or three days, although it must be admitted that a longer interval is possible. The difficulty lies in the fact that such hemorrhages are initiated by the trauma and develop progressively, differing in this respect from the apoplectic onset of a spontaneous hemorrhage consequent to arteriosclerosis and hypertension. We are of the opinion that symptoms are likely to become manifest within a week or ten days at the latest and that the longer this interval the less likely it is that the hemorrhage is of traumatic origin.<sup>20</sup>

Although true traumatic hemorrhages do occur in elderly persons and arteriosclerosis *per se* does not seem to be a predisposing factor, an apoplectic onset of symptoms with gross hemorrhage into the region of the basal ganglia in a person with arteriosclerosis and hypertension is to be considered as spontaneous even though the patient may have sustained an incidental injury some time before. One must also not be misled by minor injuries to the head in falls as a consequence of the "stroke." Moreover, this and other studies have shown that the internal capsule is less apt to be injured by blunt trauma than any other part of the brain. Although, to be sure, the lenticular nucleus has rarely been the seat of a traumatic hemorrhage, the lesion is small and is insufficient to bring about the patient's death. These facts should assist materially in distinguishing between traumatic and spontaneous hemorrhage.

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<sup>20</sup> These intervals of survival are for fatal cases. No doubt such intervals may be longer in nonfatal cases. Our study furnishes no clue as to how long this interval may be.

Even in the presence of advanced arteriosclerosis, severe injury to the head has usually resulted in marked contusion of the brain rather than in intracerebral hemorrhage. No hemorrhages into the internal capsule have been observed. In cases of arteriosclerosis observed by us in which secondary and primary intracerebral hemorrhage had occurred, no instance of gross hemorrhage into the internal capsule or other portions of the basal ganglions was observed.

In conclusion, certain deductions may be drawn from observations on cases of verified traumatic intracerebral hemorrhage which are of value in the solution of this problem. Whether or not these principles are to be dignified as postulates, they at least rest on the solid basis of morbid anatomy. These principles regarding delayed traumatic hemorrhage may be stated as follows: 1 Hemorrhage into the brain after trauma may occur in young adults as well as in older persons. 2 Except for less common instances of laceration of the brain by direct injury, traumatic intracerebral hemorrhage is the result of the *coup-contrecoup* mechanism, the injury being sustained with the head in motion. 3 Clinical symptoms of the presence of hemorrhage usually become manifest within a few days, although the patient may survive for a considerable time. 4 The lesion is commonly found in the frontal or the temporo-occipital region and is relatively superficial rather than deep in the basal ganglions. (When the ganglionic region is involved, as it is at times in injury to the sides of the head, the lesions are usually small in the lenticular nucleus or more extensive in the external, not the internal, capsule.) 5 The hemorrhage may be primary, arising within the centrum, or secondary to severe contusions of the frontal or the temporal lobes. 6 Other signs of injury to the brain (such as contusions) are almost invariably present. 7 The lesion is commonly fatal, death being due to its presence or in part to other, associated traumatic lesions of the brain. In some instances recovery may take place on surgical evacuation of the clot if other severe lesions are not present.

Although, no doubt, exceptions to these rules may occur and atypical cases are encountered in which it may be difficult to make an absolute decision, in the great majority of instances, particularly when an opportunity is given to examine the brain, a definite conclusion can be reached as to whether the hemorrhage is truly of traumatic origin or is spontaneous.

#### SUMMARY AND CONCLUSIONS

In order to evaluate Bollinger's conception of delayed post-traumatic apoplexy, a study was made of some 38 cases of gross hemorrhage into the brain substance occurring as the direct result of trauma.

Except for 3 cases of gross hemorrhage resulting from direct laceration of the brain, a traumatic hemorrhage proved invariably to be a



typical *coup-contrecoup* effect of injury, in which the head in motion struck an immobile or relatively immobile object

Two varieties of traumatic intracerebral hemorrhage are described. The first type is adjacent, or secondary, hemorrhage which is a part of a contusion of the temporal and frontal lobes which provokes it and is of no special clinical significance. The second variety is primary, or central, hemorrhage occurring in the centrum of the frontal or temporal lobes (rarely, in the less extensive form, in the external capsule and the ventricular nucleus). Central hemorrhages of the frontal and temporal lobes may reach such proportions as to assume clinical importance.

Such hemorrhages, particularly those occurring in the temporal or temporo-occipital centrum, become manifest clinically after an interval of lucidity or may pursue a progressive course in a patient who has never been rendered entirely unconscious. In such cases the clinical course mimics closely that of interval dural hemorrhages. When such hemorrhages are excessive, ultimate rupture into the ventricles or into the subdural space seems to be the rule. In the latter instance these subdural accumulations of blood may be mistaken for primary subdural hemorrhages.

Hemorrhages into the region of the basal ganglions following trauma apparently are limited to small hemorrhages occupying slitlike cavities in the external capsule or to small globular hemorrhages into the globus pallidus (the lenticular nucleus). No example of gross hemorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis, has been observed by us. It may, therefore, be safely assumed that gross hemorrhage in this region is not the result of trauma, for, of all portions of the brain presenting evidences of injury, this particular region seems to be most notably free.

Arteriosclerosis in itself does not seem to play an important part in the production of these hemorrhages, although it may have mild predisposing influence. There seems to be no greater incidence of gross intracerebral hemorrhage in persons with advanced arteriosclerosis and associated severe injuries than in younger adults. Other, rarer conditions, such as hypoplasia of the arteries or other vascular disease, may play a minor role in the production of post-traumatic hemorrhages. As far as our experience goes, syphilis seems to be of no influence whatever as a predisposing factor in the production of immediate or delayed hemorrhages.

The basic principles by which presumed instances of delayed traumatic hemorrhage are to be evaluated are briefly outlined.

## EWING'S SARCOMA (ENDOTHELIAL MYELOMA)

J F HAMILTON, MD

MEMPHIS, TENN

The subject of Ewing's sarcoma continues to hold the interest of the medical profession, especially of those members of it who see more than the casual patient with the disease. There are several reasons for this: (1) difficulties in diagnosis, since clinically and roentgenographically the tumor closely resembles other pathologic entities, (2) the fact that the cause is still obscure, (3) the fact that the mortality rate is excessive, and (4) the fact that present methods of treatment are deplorably ineffective. With these problems confronting them, physicians must disseminate the available information in an effort to reduce errors in diagnosis and must constantly strive to make earlier diagnoses. In order to accomplish these objectives, it is essential, first, that the physician inform himself better of the nature and behavior of Ewing's sarcoma and, second, that the lay public be impressed with the necessity of seeking early medical advice concerning symptoms referable especially to the extremities, particularly of persons between the ages of 5 and 20 years. Finally, the search for an ideal method of treatment must be continued.

Prior to Ewing's<sup>1</sup> history-making announcement, in 1921, of the term "diffuse endothelioma of bone" to designate the tumor under discussion, which he believed to be a definite entity, many articles had appeared in the literature pertaining to this disease. Up to that time it had been referred to by many writers as "a small or large round-celled sarcoma." Gross,<sup>2</sup> in 1879, wrote a classic paper on the subject "Sarcoma of Long Bones." There can be no doubt that he referred, in some cases at least, to Ewing's sarcoma when he described a "central and subperiosteal round-celled sarcoma."

There are still too many errors in diagnosis to permit an accurate estimation of the number of cases of endothelial myeloma from reports in the literature. The report of the Bone Sarcoma Registry for October

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Read at the Third International Cancer Congress, Atlantic City, N. J., Sept. 14, 1939.

1 Ewing, J. Diffuse Endothelioma of Bone, Proc. New York Path. Soc. 21: 17, 1921.

2 Gross, S. W. Sarcoma of the Long Bones, Based upon a Study of One Hundred and Sixty-Five Cases, Am. J. M. Sc. 78: 338, 1879.

1938 recorded 236 registered cases. Twenty-five of these were submitted from this clinic, and an additional 3 were submitted as cases of Ewing's sarcoma but were not so classified by the registry. One of the 3 (case 3, table 1) was unclassified, the committee suggested diagnoses of lymphosarcoma, myeloma, osteomyelitis and Ewing's tumor. The patient died four years after admission to the clinic and eight years after the onset of symptoms of intercurrent infection incident to metastasis to the spine, followed by paraplegia. The second case (case 20, table 1) was not classified officially but the diagnosis was regarded as



Fig 1 (case 10, table 1) —A, anteroposterior and lateral roentgenograms taken May 20, 1931, showing partial destruction of the lower end of the tibia, lifting of the upper end of the tumor and fungating tumor growth through anterior and posterior wounds made for osteomyelitis. The patient, E. L., was 12 years of age. B, telerontgenogram of the lungs taken July 10, 1939, eleven months after the first appearance of symptoms in the chest (over several years after the first admission, 5-20-31), showing a large tumor mass in the upper right lung field.

"chronic inflammation." The patient died two years later of an endothelial myeloma of the jaw with metastases to the lungs and liver. The third case (case 37, table 1) was classified as an example of osteogenic sarcoma, the opinion of the committee, however, was divided. The tumor regressed under roentgen therapy, but the patient died of metastasis to the head three and one-half months after admission. No report is available on 9 of the 28 cases submitted.

There is considerable confusion among writers regarding many phases of the endothelioma group of tumors in general and of bone tumors in particular. The endothelioma "dumping ground" has diminished to some extent, however especially since Ewing described the tumor known

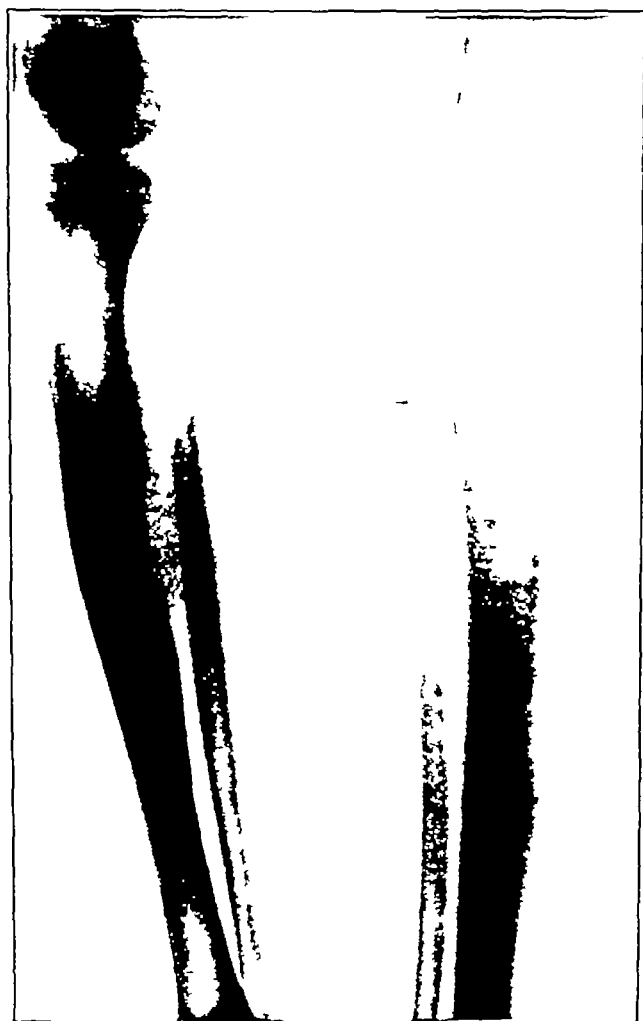


Fig 2 (case 13 table 1)—Roentgenogram in the case of E. C. aged 12. The film taken Dec. 29, 1933, shows condensation and destruction of the tibial cortex with lipping and radiating new bone.

by his name. He divided endothelioma into three types: (1) multiple endothelioma, (2) solitary angioendothelioma, and (3) diffuse endothelioma, or Ewing's sarcoma. The original Sarcoma Registry classification embraced only two types: (1) angioendothelioma and (2)

TABLE 1—Data on Twenty-Nine Cases of Ewing's Sarcoma and Eight Cases of Probable Ewing's Sarcoma

No	Patient	Admission Date	Age	Sex	Symptoms and Comment	Duration of Symptoms	Operation for Osteomyelitis		Roentgen Findings	Sarcoma Registry		Treatment	Duration of Tumor	
							Trauma	Physical Findings		Diagnosis	Committee Opinion		After Admission	Total
1	F R	2/ 2/27	7	F	Pain fever tumor	6 months	No	Swelling above lower ½	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Roentgen therapy	Died, 3 years, 5 months	3 years, 11 months
2	A L M	2/17/27	47	M	Pain, tumor	1 year	No	Tumor ankle lower ½	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Amputation, 2/18/27	Living 8 years, 3 months	9 years 3 months
3	I N D	7/ 9/27	51	F	Pain tumor	4 years	No	Swelling knee tenderness, upper ½ tibia	Condensation	Unclassified	Lymphosarcoma, myeloma, osteomyelitis	Drainage, 7/16/24, excision, 1/11/28, roentgen therapy	Died 4 years 8 years	8 years
4	S C S	10/18/28	13	F	Pain limp fever mass in groin	8 months	No	Firm, tender mass above pelvic brim lower ½	Osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy	Died 7 months 1 year 3 months	1 year 3 months
5	B A W	1/13/29	16	M	Pain, swelling	6 months	No	Firm, tender mass	Condensation, osteolysis	Ewing's sarcoma	Agreed	Roentgen therapy	Died 5 months 11 months	11 months
6	I S	2/11/30	13	F	Pain	1 year	Yes, 2	Tumor, 2 operable scars lower ½	Osteolysis, onion peel	Ewing's sarcoma	Agreed	Amputation, 2/17/30	Died 1 year, 6 months	2 years 6 months
7	K H	7/25/30	52	F	Pain tumor	3 years	No	Firm, tender mass middle ½	Condensation	Ewing's sarcoma	Melanoma, carcinoma, sarcoma	Amputation, 8/1/30	Died 5 months 3 years 5 months	3 years 5 months
8	I O P	8/ 3/30	21	M	Pain fever	4 months	Yes	Swelling	Condensation	Ewing's sarcoma	Ewing's sarcoma osteomyelitis	X-ray, Coley's toxins, 18 months	Living 9 years 4 months	9 years 4 months
9	W W M	8/29/30	9	M	Pain soreness in left groin	1 year	No	Firm, tender mass	Osteolysis pathologic fracture	Ewing's sarcoma	Agreed	Excision, 9/1/30 roentgen therapy	Died 8 months 1 year 8 months	1 year 8 months
10	I L	7/20/31	12	F	Pain swelling	2 years	Yes, 2	Fungating tumors, anterior and posterior	Osteolysis, onion peel	Ewing's sarcoma	Ewing's sarcoma osteogenic sarcoma	Amputation, 5/20/31 roentgen therapy, Coley's toxins, 6 months	Living 8 years metastasis to lung 1 year ago	10 years
11	W P S	7/11/32	20	F	Recurrent pain	1 year	No	Tenderness	Condensation	Ewing's sarcoma	Agreed	Amputation, 2/14/33 roentgen therapy	Died 1 year, 5 months	2 years, 5 months
12	I G	11/21/32	10	M	Pain in leg, knee and thigh fever	5 months	No	Mass, upper ½ of thigh	Osteolysis, onion peel, pathologic fracture	Ewing's sarcoma	Agreed	Roentgen therapy, Coley's toxins ½ months	Died 11 months 1 year 1 months	1 year 1 months
13	I C	12 29/33	12	M	Tumor roentgen therapy	2 years	No	Firm tender mass	Condensation onion peel sun ray erosion	Ewing's sarcoma	Agreed	Amputation 12/29/33, Coley's toxins (250 doses)	Living 6 years 8 years	8 years

14	I	H	7/21/71	10	F	1 min tumor fever, loss of weight	5 months	R 7th rib	No	No	Tumor R axilla	Osteolysis	I wing s sarcoma	Agreed	Roentgen therapy	Died 1 year	1 year 5 months
15	M	B	1/13/30	20	I	Recurrent rheumatism pathologic fracture August 1935 continued pain mass	2 1/2 years 8 months	I humerus upper 1/2	No	No	Visible tumor	Osteolysis onion peel	I wing s sarcoma	Agreed	Coley's toxins 10 months resection, 6/15/39	Died 2 years, 3 months	5 1/2 years
16	I	S	3/20/25	11	M	Pain tumor	2 years	I humerus, middle and lower 1/2	No	Yes	I arse fusiform tumor	Condensation onion peel scurry	I wing s sarcoma	Agreed	Amputation 1/11/25 roentgen therapy	Died 11 months	2 years 11 months
17	A	S	6/12/30	12	M	Pain fever swelling	5 months	I olecranon	No	Yes	Swelling, ankle and heel	Condensation on	I wing s sarcoma	Agreed	Amputation 9/9/35 roentgen therapy	Died 1 year, 2 months	1 year 7 months
18	H	G	10/29/25	21	M	Resection 4 ribs August 1922 roentgen ther- apy pain swell- ing of R thigh	1 years 1 year	6th to 9th ribs, R R femur, upper 1/2	No	No	Swelling, upper 1/2 of thigh	Condensation osteolysis	I wing s sarcoma	Agreed	Roentgen therapy Coley's toxins 3 months	Died 1 year 9 months	5 years 9 months
19	I	G	8/7/30	11	M	Pain in R hip fever, biopsy, October 1935 diagnosis sar- coma roentgen therapy	1 year	R ilium	No	No	Firm mass	Condensation	I wing s sarcoma	No report	Roentgen therapy	Died 8 months	1 year 8 months
20	O	K	1/6/17	17	M	Pain swelling abscessed teeth 1 years pre- viously	1 weeks	R mandible	Yes	No	Swelling, R gum draining sinus	Osteolysis	Chronic inflam- mation	No report	Curettage roent- gen therapy	Died 2 years 1 month	5 years 1 month
21	B	J	5/13/17	0	I	Pain tumor	6 months	I tibia upper 1/2	Yes, 2	Yes	Nodular infected tumor, upper 1/2 of t leg	Osteolysis onion peel, scurry	I wing s sarcoma	No report	Amputation 7/2/17 roentgen therapy	Died 7 months	1 year 1 month
22	I	M	6/11/17	22	I	Tender swelling in t axilla roentgen ther- apy regression	6 months	I 10th rib	No	No	Tender swelling, over 8th to 10th ribs	Osteolysis, onion peel metastasis to lung	I wing s sarcoma	No report	Roentgen therapy	Died 3 months	9 months
23	I	I	0/7/17	21	M	Tumor roent- gen therapy, regression	8 months	I tibia, middle 1/2	No	No	Firm mass	Condensation	I wing s sarcoma	No report	Amputation, 9/8/17 roentgen therapy Coley's toxins 18 weeks	Died 1 year	1 year 8 months
24	I	M	0/15/17	4	I	Pain limp fever swelling biopsy 1 year previously	2 1/2 years	R tibia upper 1/2	No	No	I uniform swelling	Osteolysis onion peel scurry	I wing s sarcoma	No report	Amputation 9/18/17 roentgen therapy	Died 1 year 2 months	1 years 8 months
25	B	I	10/27/17	10	F	Pain in t knee ilium	2 1/2 years	I ilium, pos- terior aspect	No	No	Firm tender mass	Osteolysis with osteitis	I wing s sarcoma	No report	Roentgen therapy	Died 4 months	2 years 10 months

TABLE 1—Data on Twenty-Nine Cases of Ewing's Sarcoma and Eight Cases of Probable Ewing's Sarcoma—Continued

No.	Patient	Admission Date	Age	Sex	Symptoms and Comment	Duration of Symptoms	Operation for Osteomyelitis	Site	Trauma	Physical Findings	Roentgen Findings	Sarcoma Registry		Duration of Tumor	
												Diagnosis	Committee Opinion	After Admission	Total
26	W A F	1/7/38	47	F	Pain in R knee	4 months	No	R femur, lower $\frac{1}{2}$	No	Slight tenderness, R knee	Osteolysis	Ewing's sarcoma	No report	Amputation, 2/16/38, roentgen therapy	Died 6 months 10 months
27	L M	7/8/37	15	F	Pain, loss of weight	9 months	No	Sacrum	No	Firm, tender mass	Osteolysis	Ewing's sarcoma	No report	Roentgen therapy	Died 1 year, 3 months 2 years
28	M H	12/23/38	30	F	Pain, tumor, fever, radium and roentgen therapy	3½ years	Yes	R femur, middle $\frac{1}{3}$	No	Tenderness, lower $\frac{1}{2}$ of thigh, old operative scar	Condensation, sunray, erosion			Roentgen and radium therapy, amputation, 1/2/39	Living 8 months 4 years 2 months
29	H S (Negro) John Gas ton Hospital	2/20/37	11	M	Pain, swell ing fever	4 months	No	Mandible	No	Swelling incisor region	Osteolysis			Excision, 2/23/37	Died, 4 months 8 months
Probable Ewing's Sarcoma															
30	G F	5/21/21	13	M	Pain, fever	4 months	No	R femur, upper $\frac{1}{3}$	No	Firm, tender mass	Osteolysis, onion peel			Amputation, 5/26/21	Died 6 months 9 months
31	M L L	2/10/23	7	F	Pain swell ing, L knee and thigh	3 months	No	L femur, lower $\frac{1}{3}$	No	Irregular swelling	Osteolysis, onion peel			Amputation, 2/14/23	
32	I B	10/30/23	15	F	Pain fever	3 months	No	R femur, upper $\frac{1}{2}$	Yes	Swelling	Osteolysis, onion peel			None	Died 4 months 7 months
33	I C	11/15/26	14	M	Pain fever	4 months	Yes	R femur, upper $\frac{1}{3}$	No	Swelling	Osteolysis, onion peel			Drainage	Died 4 months 8 months
34	I T	5/25/27	6	M	Pain, swell ing	1 month	No	I femur, lower $\frac{1}{2}$	Yes	Swelling	Osteolysis, onion peel			Amputation, 7/1/27	Died 10 months 11 months
35	A C	2/8/32	17	1	Pain in back and legs	6 months	No	1st and 2d L vertebrae	Yes	Slight kyphosis tenderness, 2d lumbar vertebra partial paraplegia	Negative			I aminectomy roentgen therapy	Living 7 years, 6 months 8 years
36	N H	7/9/35	21	M	Pain swell ing right thigh drainage Oct 1934 roentgen therapy, re excision	2 years	Yes	R ischium	No	Swelling	Condensation periosteal reaction metastasis to lung				Died 2 months 2 years 2 months
37	I A	9/10/11	13	F	Pain swell ing	3 months	No	I ilium	No	Swelling	Osteolysis	Osteo- genic sarcoma	Osteo- genic sarcoma metastatic tumor	Roentgen therapy Coley's toxins	Died 4 months 7 months

diffuse endothelioma In the revised classification of the registry for 1939 the aforementioned grouping was not changed In a recent article, however, Ewing<sup>3</sup> stated

According to the present available observations, it seems desirable to recognize a special class of bone tumors arising from blood vessels with varying structure and degrees of malignancy as follows

- A Cavernous angioma
- B Plexiform angioma (sun-ray radiological type)
- C Angio-endothelioma with fine blood channels lined by single rows of endothelial cells
- D Diffuse endothelioma, with pseudorosettes and perithelial units (Ewing's sarcoma)

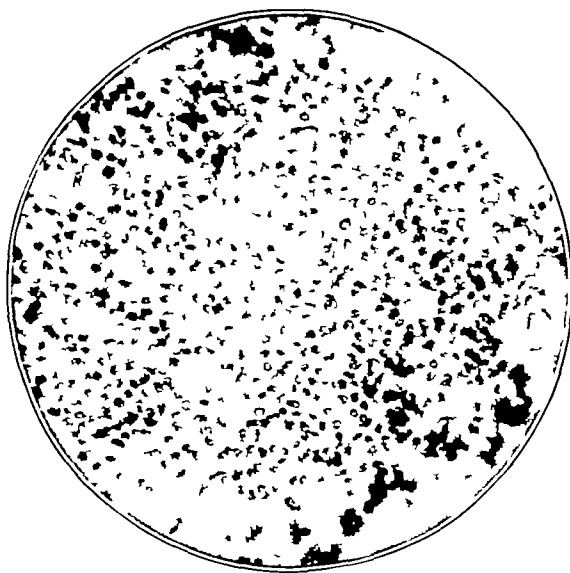


Fig 3—Photomicrograph of the tumor of E C (fig 2), showing a solid sheet of cells The cytoplasm is not shown, the nuclei are small, oval to round and moderately deeply stained Nucleoli and mitoses are present.  $\times 430$

The gross appearance of the tumor varies, of course, according to its age, its location and the character of its blood supply The subperiosteal tumor, if examined before extensive hemorrhage and necrosis have occurred, is firm, rubber-like and covered by a capsule Its cut surface appears moist, grayish white and semitranslucent, it is divided into lobules by connective tissue trabeculae and tends to well out In the presence of necrosis, bone lysis and hemorrhage, on the contrary, the tumor has no form and may closely resemble purulent exudate This type is commonly observed in the flat bones

<sup>3</sup> Ewing, J A Review of the Classification of Bone Tumors Surg, Gynec & Obst. 68 971, 1939



Ewing has stated that when microscopic study of a tumor reveals cells in sheets without intercellular stroma, usually with small vesicular nuclei, the cells often enclosing small or large blood spaces which contain intact and apparently circulating blood, one is justified in making a

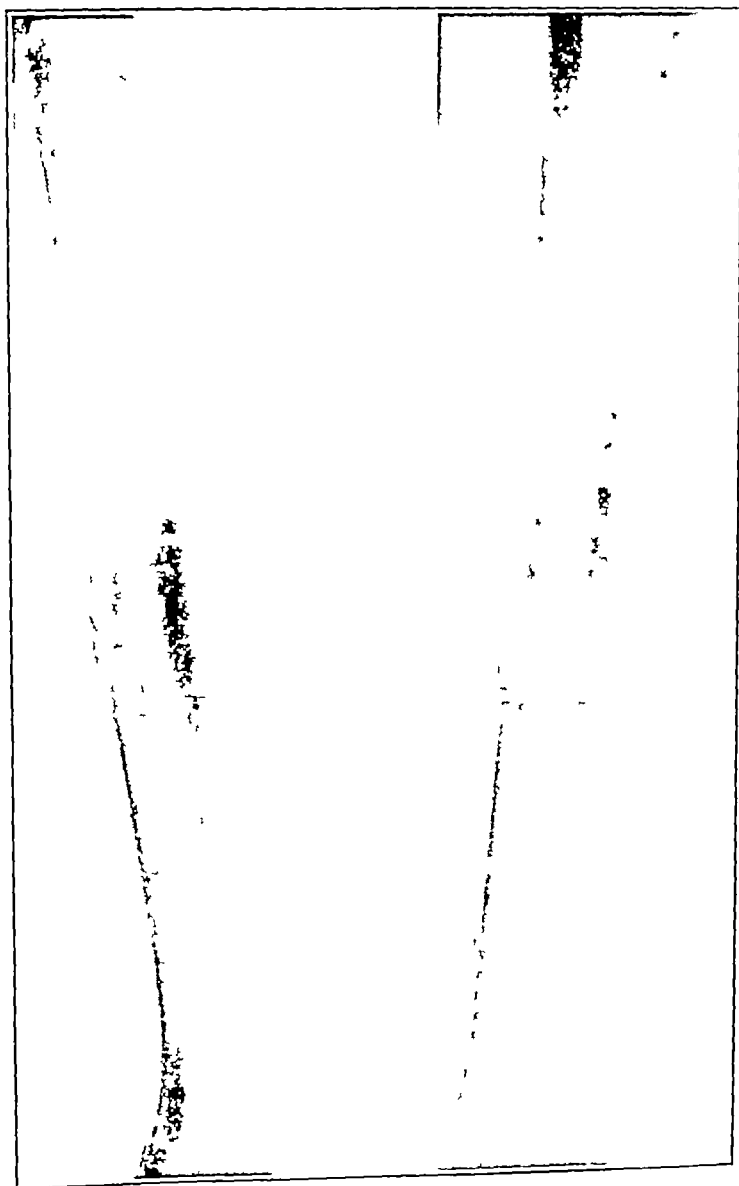


Fig 4 (case 16, table 1) —Roentgenogram in the case of J S Jr, aged 11. The left humerus (March 27, 1935) shows condensation and destruction of the cortex, parallel and perpendicular new bone formation and infiltration of the soft tissues.

diagnosis of endothelioma. The vast majority of the tumors of our series were of this type. The usual microscopic appearance was that of solid, compact sheets of polyhedral cells with small, moderately

stained vesicular nuclei of fairly uniform size and round or oval shape. The limiting membrane of the nucleus was well outlined. The chromatin was finely granular, though chromatin knots were often seen. It is impossible to state whether some of these chromatin knots were not in reality nucleoli. The cytoplasm was scarce and when stained (hematoxylin and eosin) was neutral to acidophilic. In several of the specimens removed at some time after an operation for osteomyelitis, however, the nuclei of the cells were much larger and more vesicular and contained large chromatin knots or nucleoli. In case 8 (table 1), for example, the nuclei were so large that I regarded the tumor as an osteogenic sarcoma.



Fig 5—Photomicrograph of tumor of J S Jr (fig 4), showing tumor cells in the vascular spaces between new bone spicules. The circled area is shown in figure 6.  $\times 100$

until a decided and lasting response to roentgen therapy convinced me of my error. Thus, it is important that the pathologist keep in mind the pleomorphic character of some biopsy specimens, particularly those taken after a previous operation.

The origin of Ewing's sarcoma is still questionable, what is known regarding its histogenesis is based on conjecture. Melnick<sup>4</sup> and Oberling and Raileanu have stated that the tumor arises from undifferentiated

<sup>4</sup> Melnick, P J. Histogenesis of Ewing's Sarcoma of Bone, *Am J Cancer* 19 353, 1933.



Fig 6—4, photomicrograph of the circled area in figure 5, showing tumor cells which appear to be forming a lining for the vascular spaces  $\times 1,000$  B, photomicrograph (same case) showing a solid sheet of polyhedral cells. The nuclei are irregular in size and shape and are moderately deeply stained. There is an occasional nucleolus and mitotic figure. The cytoplasm is palely stained. There is no intercellular stroma  $\times 1,000$

embryonic mesenchymal cells about the blood vessels in the haversian canals Connor<sup>5</sup> and Ewing<sup>6</sup> at first believed that the disease arose in the marrow cavity Ewing qualified his opinion, however, by stating that it begins in the blood vessels of the bone tissue He further



Fig 7 (case 17 table 1) — *A*, roentgenogram in the case of *A S*, aged 12 The film, taken June 12, 1935, shows increased density (probably the earliest roentgen change to Ewing's sarcoma) of the right calcaneus *B*, roentgenogram taken on August 26, showing a destructive osteomyelitis-like lesion of the right calcaneus

<sup>5</sup> Connor C L Endothelial Myeloma, Ewing Report of Fifty-Four Cases Arch Surg 12 789 (April) 1926, A Further Consideration of Ewing's Sarcoma Am J Cancer 22 41, 1934

(Footnotes continued on next page)

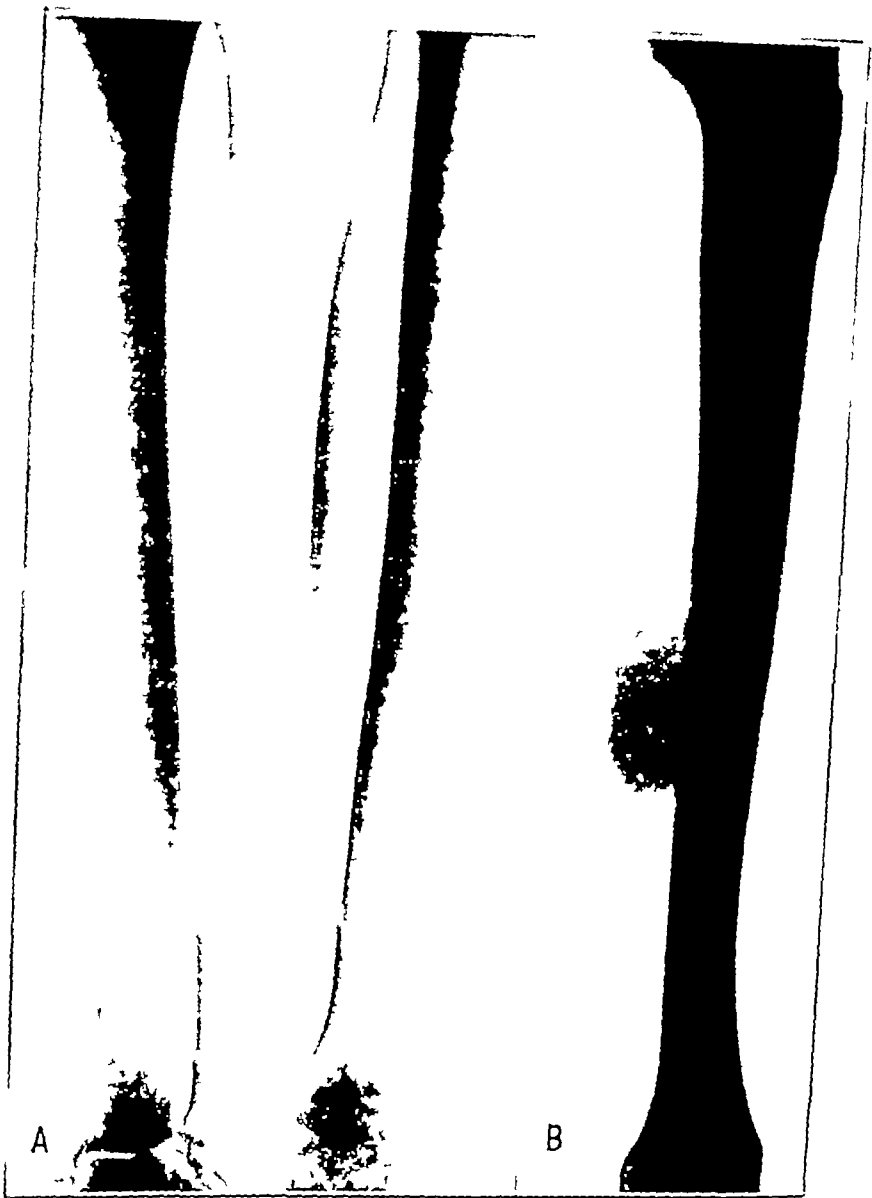


Fig 8 (case 23, table 1) — *A*, roentgenogram in the case of J S, aged 21. The film, taken Sept 3, 1937, shows condensation of the cortex of the middle third of the left tibia. *B*, roentgenogram in the same case, showing the specimen after the soft tissues had been removed. The tumor is attached to the tibia. Note also a cordlike growth of the tumor which followed the course of the tibial tendon to ankle.

6 Ewing, J. Further Report on Endothelial Myeloma of Bone, Proc. New York Path Soc 24 93, 1924, Endothelioma, in Neoplastic Diseases, ed 3, Philadelphia, W B Saunders Company, 1928, p 328, footnotes 1 and 3.

(cases 17 and 18, table 1) Malignant cells have been observed, apparently lining the spaces. Geschickter and Copeland<sup>7</sup> also concluded that the growth arises from lymphatic endothelium but attributed to it an intracortical or subperiosteal origin, while Kolodny<sup>8</sup> regarded the tumor as developing from the coalescence of multiple foci in the medulla and cortex. That Ewing's sarcoma may be of multiple origin has not been disproved. Indeed, Ewing himself stated "It is difficult to determine whether the multiple tumors which are found, as indicated by clinical signs and radiographs, are metastases or multiple primary tumors. I have been unable to reach any conclusion, but the very extensive distribution of tumors in the late stages and the comparative integrity of the other organs lead one to think that the dissemination of the disease is mainly from multiple primary tumors developing throughout the bony system." The tumor in case 26 (table 1) appeared to be of a multiple medullocortical origin. The first roentgenogram, made four months after pain was first experienced in the knee, revealed a worm-eaten appearance of the lower femoral metaphysis with extension to the epiphysis. The patient was 47 years old. An amputation was carried out through the upper third of the right thigh, far above any clinical or roentgen evidence of the tumor in the lower third. To my surprise, tumor cells were found in the marrow cavity, within 1 cm. of the distal amputated end. A course of roentgen therapy was immediately begun and was followed by disarticulation at the hip joint. The patient died of metastases to the opposite femur and elsewhere five and one-half months after the first amputation.

Colville and Willis<sup>9</sup> expressed the opinion that many of the growths classified as Ewing's sarcomas would, on careful investigation, prove to be metastases from neuroblastomas. Hirsch and Ryerson<sup>10</sup> stated the belief that Ewing's tumor has been confused with metastatic bronchogenic carcinoma of bone. These opinions may have some truth in them. Postmortem examination in 1 of my cases (case 15) revealed tumor tissue in the left adrenal gland. My associates and I do not believe, however, that this tumor arose in the adrenal gland, our reasons for this opinion were explained in a report of the case.<sup>11</sup> Furthermore,

7 Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*, ed. 2, New York, American Journal of Cancer, 1936.

8 Kolodny, A. *Bone Sarcoma. The Primary Malignant Tumors of Bone and the Giant-Cell Tumor*, Surg., Gynec. & Obst. (supp. 1) **44**: 1, 1927.

9 Colville, H. C., and Willis, R. A. *Neuroblastoma Metastases in Bone, with a Criticism of Ewing's Endothelioma*, Am. J. Path. **9**: 421, 1933.

10 Hirsch, E. F., and Ryerson, E. W. *Metastases of the Bone in Primary Carcinoma of the Lung*, Arch. Surg. **16**: 1 (Jan., pt. 1) 1928.

11 Campbell, W. C., and Hamilton, J. F. *Endothelial Myeloma. Case Report with Necropsy*, J. Bone & Joint Surg. **20**: 1019, 1938.

too many postmortem reports have been made of Ewing's sarcoma without involvement of the adrenal glands to permit any question of the existence of this tumor. Studies of many microscopic sections made from blocks of tumor in cases 11, 13, 16, 17, 23 and 24 (table 1) incline one to believe that the tumor arises in the perivascular lymph vessels, provided, of course, that it has a single primary origin.

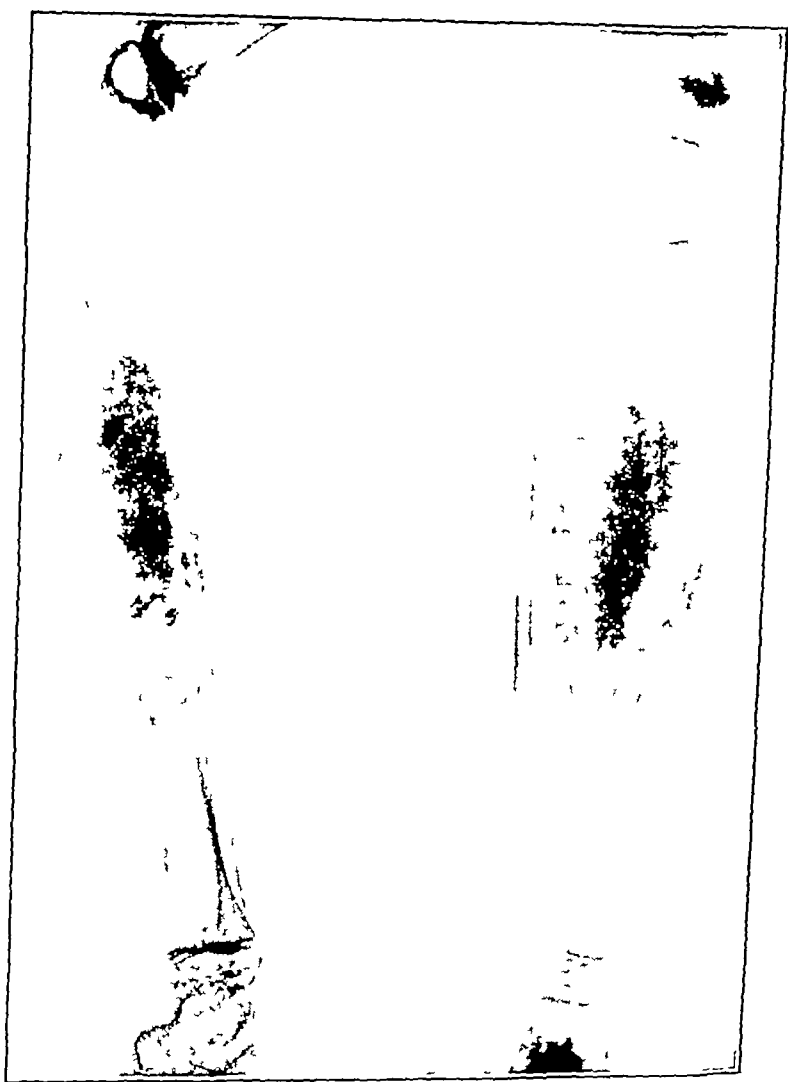


Fig 9 (case 24, table 1) —Roentgenogram in the case of J W, aged 4 years. The film, taken Sept. 15, 1937, shows a fusiform tumor of the right tibia with lifting and marked perpendicular striation of reactive bone. The general outline of the tibia is well preserved.

In this connection, Geschickter and Copeland referred to Ewing's sarcoma of the soft parts adjacent to the periosteum. I have observed 2 cases of fibrosarcoma arising from the soft tissues of the thigh in which the cytologic picture closely resembled that of endothelial myeloma. These cases are not included in the group reported.

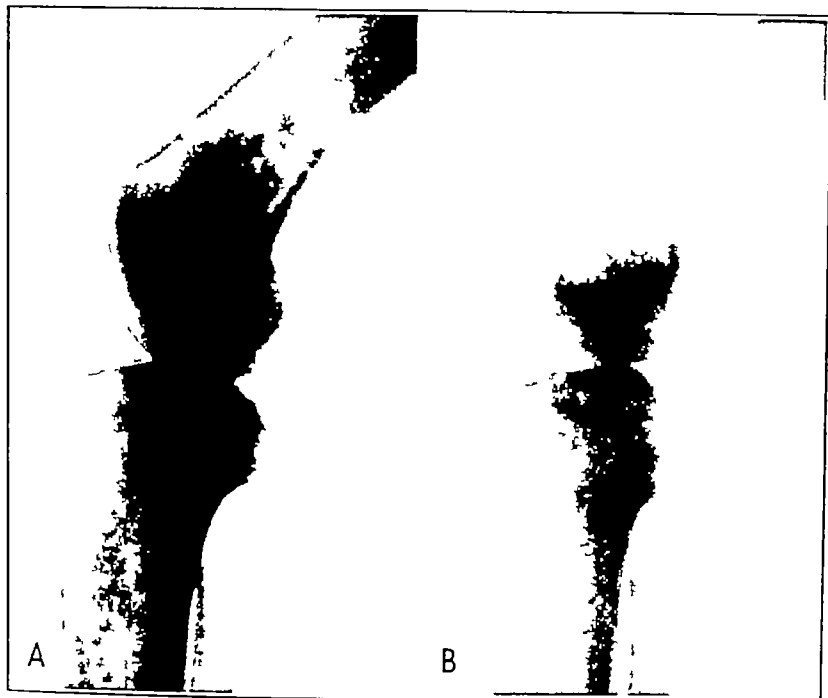


Fig 10 (case 26, table 1)—A, roentgenogram in the case of W F, aged 47. The film, taken Jan 7, 1938, shows a mottled destructive lesion of the medulla and cortical portions of the lower third of the right femur without periosteal reaction. B, roentgenogram (same case) taken January 31, shows slightly more destruction of bone than is observed in A.

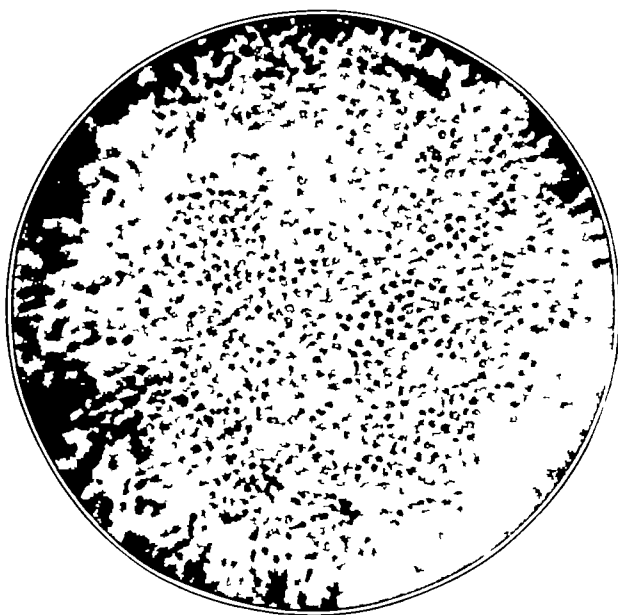


Fig 11—Photomicrograph of the tumor of W F (fig 10), revealing a solid sheet of tumor cells. The nuclei are round to oval, fairly uniform in size and moderately deeply stained. The cytoplasm is not visible. Mitoses are present. There is no intercellular stroma.  $\times 430$



The cause of Ewing's sarcoma, like its site of origin, is unknown. In my opinion, the theory of embryogenic disturbance, whether chemical or hormonal, is as well founded as the theories of an infectious or traumatic cause.

The diagnosis must rest on a carefully taken history, attention being given to details, and on the physical, roentgen and pathologic findings. Every patient should be closely studied with the following signs and symptoms in mind:

Intermittent attacks of pain, with or without swelling and fever, in a flat bone or in the shaft of a long bone, lasting in the beginning only a few days to a week or two, with the intervals between attacks gradually becoming shorter until the patient is forced to seek medical advice, are highly suggestive of Ewing's sarcoma. Especially is this true of persons less than 20 years of age. During the remissions the patient may feel entirely well and may have normal use of the affected part. The growth of the tumor may be so insidious that advanced changes may be observed in the first roentgenogram of the bone. Indeed, a pathologic fracture may take place before the patient comes for roentgen study. A case in point was case 15 (table 1).

The pain may be explained on the basis of intraosseous or subperiosteal pressure from growth of the tumor or from hemorrhage. I have found no suggestion in the literature of the probability that hemorrhage may be responsible for the pain. This, however, is quite likely, particularly in the acute attacks of the early stages. Moreover, hemorrhage may well cause the fever and leukocytosis. The patients have no fever or leukocytosis during the painless intervals of the clinical course, even though the tumor continues growing, whereas a leukocyte count of from 12,000 to 15,000 per cubic millimeter may be found during an attack of acute pain and fever. Leukocytosis with little, if any, alteration in the differential blood count may be of some significance. Such a blood picture has been observed, though in too few patients to permit any conclusion. This type of hemogram is not consistent with the infectious theory of histogenesis.

All of our patients had a negative Wassermann reaction. No Bence Jones bodies were found in any of the urinalyses.

Loss of weight and appetite are late manifestations of the disease. The pulse rate is believed to be accelerated so long as growth of the tumor is active. This has proved a valuable prognostic sign in my experience, leading me to suspect concealed metastases, especially in patients who return for observation after initial therapy. If the tumor is in the shaft of a long bone, a firm, fixed tender mass may or may not be palpable, soft tissue reaction and swelling may obscure the tumor,

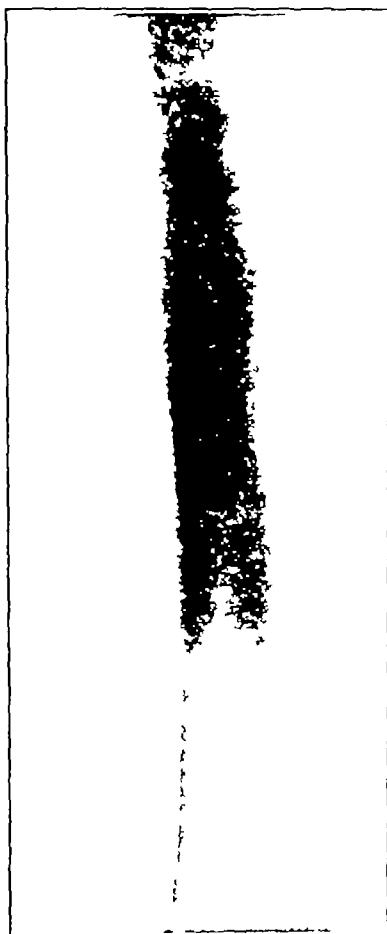


Fig 12 (case 28, table 1)—Roentgenogram in the case of M H, aged 30. The right femur (Dec 28 1938) reveals condensation, destruction and spicules of reactive bone.

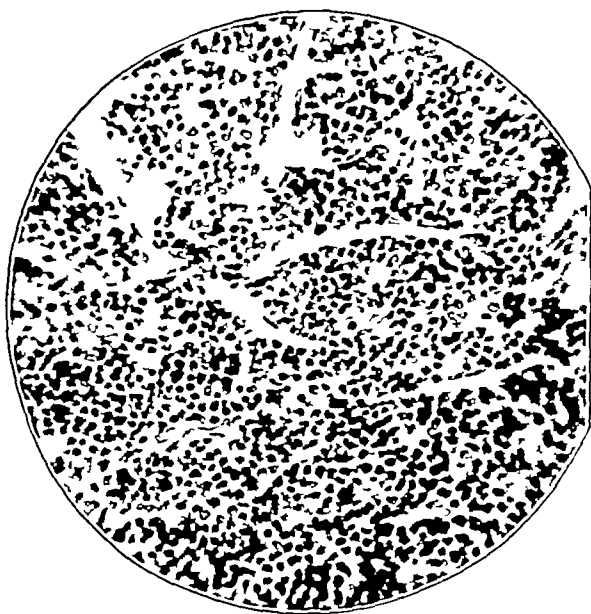


Fig 13—Photomicrograph of tumor of M H (fig 12) reveals solid sheets of small round cells divided into lobules by fibrous connective tissue trabeculae. The nuclei are small, round to oval and fairly uniform in size. Cytoplasm is not visible. Mitoses are present. There is no intercellular stroma.  $\times 430$ .

or only a questionable thickening of the shaft itself may be found. Fever is usually detected at the site of the tumor, and the superficial veins may be dilated and visible.

Roentgenograms are indispensable diagnostic agents. Condensation is the earliest roentgen evidence of Ewing's sarcoma, the involved bone reacts violently to the invasion of the disease process. This is a strong point in favor of a subperiosteal or intracortical rather than a medullary origin of the growth. Cases 8, 11, 13 and 23 (table 1) illustrate this compensatory bone reaction. In case 23 thickening and condensation were revealed by the roentgenogram, and on pathologic study of the entire circumference of the shaft of the tibia at the level of a small, elliptic subperiosteal tumor the marrow cavity was filled with a similar bone reaction. This reaction on the part of bone not only to Ewing's sarcoma but to other diseases, which makes diagnosis all the more confusing, has been known for years but was reemphasized by Campbell<sup>12</sup> as being especially apparent in young patients with this disease. He called attention to the three stages of osseous change manifested by the tumor in the roentgenogram: (1) condensation, (2) invasion, expansion, striation and destruction, and (3) disintegration of all bony structure and invasion of the soft tissues. This is probably the order of development of the growth in young bone. A number of years may be required for completion of the evolutionary pathologic process, or it may be completed within a few weeks to a few months.

I believe, with others, that the Ewing tumor cell has no part in the formation of bone. Connor,<sup>5</sup> however, stated that the parent cell of the tumor may differentiate into an osteoblast. Lipping (onion peel), so commonly seen near the junction of diseased and healthy bone in the late stage, is the remains of the parallel layers of reactive bone laid down at the time of invasion and expansion of the cortical and subcortical zones by the tumor. This is well illustrated in cases 1, 2, 6 and 10 (table 1). Radiating spicules of reactive bone lying perpendicular to the shaft, such as were found in cases 16 and 24 (table 1), are not uncommonly seen.

Some authors advocate the use of the therapeutic test by means of roentgen therapy to establish a diagnosis, regression of the tumor being highly suggestive of Ewing's sarcoma. One can imagine serious objections to this practice as a routine measure. If, however, one knew that taking a biopsy specimen would subject the patient to undue risk of metastatic spread and the technic of roentgen therapy were standardized the therapeutic test might be justified, although scientific knowledge

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<sup>12</sup> Campbell, W. C. Endothelial Myeloma, *J. Bone & Joint Surg.* **16**: 761 1934.

would suffer irreparably. The danger of spread of the tumor as a result of removal of a biopsy specimen is debatable. Some of the most eminent authorities frown on the procedure. There may be a few medical centers wherein opinion is sufficiently expert to diagnose and treat this disease without resorting to biopsy, but to endorse such a plan for general adoption would be hazardous. The time has not come when one may safely advise the sacrifice of a limb for a bone tumor which presents as many diagnostic pitfalls as Ewing's sarcoma without first having microscopic confirmation. Furthermore, the taking of biopsy specimens particularly from this tumor, has not been proved, so far as I know, to be conducive to metastasis. McLean and Sugiura<sup>13</sup> performed "needle biopsies" of a number of rat carcinomas and mouse sarcomas and in some of the animals macerated the tumor with the needle. There was no increase of metastases over those observed in a control group.

Colville and Willis<sup>9</sup> expressed the opinion that a diagnosis of Ewing's sarcoma cannot be made by microscopic sections alone. Attempts to make a diagnosis from biopsy material are indeed exceedingly hazardous. This is true especially if the tissue is removed in small particles, if necrosis is present or if only the margin (edematous envelope) of the tumor is excised. If the biopsy specimen is taken from the edematous tissue adjacent to a subperiosteal elliptic type of tumor, for example a few scattered tumor cells with more or less flattened nuclei, endothelial cells and lymphocytes may be found. Such a picture may be easily confused with inflammation. An unquestionable block of tumor tissue should be excised if the surgeon expects a rapid section diagnosis.

Ewing's sarcoma must be differentiated from (1) inflammation, (2) osteogenic sarcoma, (3) lymphosarcoma, (4) Hodgkin's disease and (5) retinoblastoma.

The roentgen appearance of the sclerosing osteomyelitis of Garre may be identical with that of Ewing's sarcoma. The presence of fever and changes in the blood and the fact that roentgen therapy may relieve pain are common to both. Biopsy and cultures will determine the diagnosis.

Syphilitic infection of the bone may produce the roentgen picture of Ewing's sarcoma, the lesions of the former, however, are often multiple in the tibia, clavicle and sternum. The age incidence of syphilis is usually beyond 30 years. The complement fixation test will differentiate the two conditions. If the reaction to the Wassermann test is positive and there is still doubt that the bone lesion is syphilitic, one should wait for the therapeutic test before taking a specimen for biopsy.

Osteogenic sarcoma is rarely seen in the shaft of the long bones. Its usual site is in the metaphysis from which it tends to invade the

<sup>13</sup> McLean J, and Sugiura, K. Does Aspiration Biopsy of Tumors Cause Distant Metastasis? *J Lab & Clin Med* 22:1254 1937

epiphysis The production of bone by the tumor is often obvious In addition, the cortex is obliterated early in the course of the disease The tumor, moreover, does not regress under roentgen or radium therapy Recurrent pain and fever are uncommon, and the duration of symptoms usually is shorter Microscopic examination seldom should offer any difficulty in the diagnosis

Primary invasion of bone by lymphosarcoma is rare The lesions are likely to be multiple Periosteal reaction takes place late, if at all, considering the degree of bone destruction Biopsy is the determining factor

Hodgkin's disease must be distinguished from Ewing's sarcoma by microscopic examination

Retinoblastoma may resemble Ewing's sarcoma clinically, roentgenographically and microscopically It is exceedingly difficult, if not impossible, to differentiate the two conditions microscopically The finding of true rosettes in retinoblastoma, although not always possible, especially in bone lesions, is a material aid, one must remember, however, that pseudorosettes may sometimes be found in Ewing's sarcoma We have observed 2 patients with retinoblastoma within the past year In both, the right eye had been enucleated approximately nine months before metastases appeared in the right ulna and the right scapula, respectively The material from one of these tumors was reviewed by a distinguished pathologist in a large medical center, who made a diagnosis of Ewing's sarcoma A portion of the same biopsy specimen was sent to the United States Army Medical Museum, where the eye had been sent nine months previously, the diagnosis from the museum was retinoblastoma with metastasis to the ulna Both patients lived only a few months

The prognosis in cases of Ewing's sarcoma, as in those of other malignant tumors, must be guarded Experience would seem to indicate that the expression "a five year cure" is erroneous, to speak of "a ten year cure" probably would be more accurate Cures usually are reported in 75 to 15 per cent of cases Three, or 10 per cent, of my 28 patients whose cases were registered have lived five years or longer without a recurrence

There is no known single or combined specific cure for the disease Administration of Coley's toxins has been defended through the years by Coley and others<sup>14</sup> as a valuable therapeutic measure Irradiation with roentgen rays and radium, followed by radical operation at the first

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14 Coley, W B Endothelial Myeloma or Ewing's Sarcoma, *Radiology* 16 627, 1931, Endothelial Myeloma, or Ewing's Sarcoma, *Tr South S A* 43 65, 1931, Endothelial Myeloma, *Am J Surg* 27 7, 1935

evidence of a return of activity of the tumor, has been proposed by Ewing. Others feel that radical operation followed by irradiation is the procedure of choice, and according to statistics this is the most successful regimen. That endothelial myeloma regresses after irradiation is well known, but the clinical behavior of the tumor and the postmortem observations support the contention that irradiation alone is not curative. The clinical course and microscopic observations in case 15 (table 1) would seem to lend strength to this opinion. The patient in this case received a total of 15,900 roentgen units. On subsequent examination of the resected humerus, viable tumor cells were revealed in the marrow cavity. Groups of two or three suggestive-looking cells were scattered through the sections made from the soft tissue at the time of operation, that these were tumor cells was evidenced by the recurrence of the tumor about the fibular graft. Brunschwig<sup>15</sup> recently denied that Ewing's tumor cells are radiosensitive, since they are not entirely destroyed.

Geschickter and Copeland reported on 2 of a group of 30 patients living five years after treatment by irradiation, alone or with exploration, 3 of a total of 29 patients living five years after resection or amputation without irradiation, and 3 of 18 who were well five years after resection or amputation and irradiation. In a recent personal communication to me, Dr. Bowman C. Crowell, of the Bone Sarcoma Registry, stated that of the 236 registered patients with Ewing's sarcoma 14 have lived from five to twenty-one years after treatment. These were among a group of 164 who were treated five or more years ago. Thirteen of the 14 patients were subjected to operation. Eight underwent amputations, and in 3 the tumor was excised. Two were treated by resection and subsequent roentgen irradiation. Of the 8 who underwent amputations 5 received Coley's toxins in addition, and 6, irradiation. Five of the 8 had undergone one or more surgical procedures prior to amputation. One of the 14 received roentgen therapy and Coley's toxins, without any operation other than removal of a biopsy specimen. One patient died of an unknown cause seven and one-half years after treatment.

Since 1920, 36 patients have been admitted to this clinic with a diagnosis of Ewing's sarcoma. Another case has been added from the records of the John Gaston Hospital, making a total of 37 cases (table 1). Of the 36 cases from the clinic, 16 (cases 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 32, 33, 34 and 35), as well as 1 other not included in this series, were reported by Campbell in 1934.

<sup>15</sup> Brunschwig, A. Radioresistant Ewing's Sarcoma of Bone, *Radiology* 27: 328, 1936.

Some of the necessary data are lacking for making a definite diagnosis in 8 of the 37 cases listed in table 1, though the data available are sufficient to justify inclusion of these as probable Ewing's tumors. For analytic purposes, however, I am considering an analysis of only the 29 patients in whose cases biopsy material is available in addition to all other necessary data.

It is an interesting fact (table 2) that 15 (51.7 per cent) of the 29 patients were between 11 and 21 years of age, 19 (65.5 per cent), under 21 years of age, and 24 (82.7 per cent) under 31 years of age. Only 5

TABLE 2—Age and Sex Incidence of Ewing's Sarcoma

Age	Number			Per Cent
	Male	Female	Total	
1-10		4	4	13.8
11-20	8	7	15	51.7
21-30	3	2	5	17.2
31-40	1		1	3.4
41-50	1	1	2	6.8
51-60		2	2	6.8
Total	13	16	29	100.0

TABLE 3—Site of Primary Lesion of Ewing's Sarcoma

Bone	Total Number of Cases	Upper Shaft	Lower Shaft	Mid Shaft
Tibia	11	2	2	7
Femur	4	1	2	1
Ilium	3			
Humerus	2	1		1
Rib	3			
Mandible	2			
Fibula	1		1	
Pubis	1			
Calcaneus	1			
Sacrum	1			

(17.2 per cent) were over 30 years of age. The youngest patient (case 24) was 4 years old when admitted but had had symptoms since the age of 1½ years. The oldest (case 7) was 52 years old when first seen, symptoms had been present for three years. The average duration of symptoms before admission in the group of 29 patients was seventeen and seven-tenths months, the shortest was four months, and the longest, forty-eight months.

Table 2 shows a sex incidence in the 29 cases of 13 males and 16 females.

A history of trauma was obtained in 6 (20 per cent) of the 29 patients. This is low compared to other statistics.

In table 3 may be seen the primary location of the tumor, as follows: tibia, 11 instances (37.9 per cent), femur, 4 instances (13.8 per cent),

ilium, 3 instances (10.3 per cent), rib, 3 instances (10.3 per cent), humerus and mandible, 2 instances each (6.9 per cent) and fibula, pubis, calcaneus and sacrum, 1 instance each (3.4 per cent). Of the 11 tumors of the tibia, 7 were in the middle third and 2 each in the upper and lower thirds. One of the tumors of the femur was in the middle third, and 2 each were in the upper and lower thirds. The 2 in the humerus were in the middle and upper thirds. The fibular tumor was in the lower third.

Five patients (cases 2, 8, 10, 13 and 28, table 1) of the 21 with a positive diagnosis of Ewing's sarcoma and 1 (case 35, table 1) of the group of 8 with a probable diagnosis of Ewing's sarcoma are living. The patient in case 2 when last heard from (1935) had lived nine years after amputation. The patient in case 8, who received irradiation and Coley's toxins, was also living nine years later. This case is most interesting. Drill holes had been made into the tibia for osteomyelitis three months before the patient's admission to this clinic. The symptoms returned. After admission a trap door was made in the tibia, for the same condition. Because of the pleomorphism and large cells observed in the biopsy specimen, I reported the presence of sarcoma, probably osteogenic. Since this was difficult for the surgeon to believe, two other biopsies were performed. The first of these specimens contained tumor cells, while the second contained none.

The patient in case 10 has lived eight years after amputation and treatment with roentgen rays and Coley's toxins. One year ago, however, seven years after operation, symptoms referable to the chest appeared. The roentgenogram disclosed a right pleural effusion and metastasis to the right lung. Irradiation is now being administered.

The patient in case 13 was living six years after amputation. The operation was both preceded and followed by irradiation, and, in addition, Coley's toxins were given postoperatively. Only nine months have elapsed since the patient in case 28 underwent an amputation. Roentgen and radium irradiation were carried out previously. The patient in case 35 of the group with probable Ewing's tumors is still living and states that she is well, seven and one-half years after admission and treatment by roentgen rays alone.

#### CONCLUSIONS

1 I believe that Ewing's sarcoma is a definite entity and that it is of vital interest to the medical profession for the following reasons: (a) diagnosis is difficult, since clinically and roentgenographically the tumor closely resembles other pathologic entities; (b) the cause is



obscure, (c) the mortality rate is excessive, and (d) present methods of treatment are deplorably ineffective

2 There are several theories of the origin of Ewing's sarcoma. It is not impossible that the disease may have a multiple primary origin.

3 The cause of the tumor is unknown.

4 The gross and microscopic appearances of the tumor are variable.

5 The high incidence of the disease in persons between the ages of 5 and 20 years is noteworthy.

6 A careful history, physical examination and roentgen study are of first importance in the diagnosis.

7 The diagnosis must rest on correlation of all available data. Microscopic confirmation of the clinical and roentgen findings is essential, especially prior to radical operation.

8 Because of the similarity of Ewing's sarcoma to other pathologic entities, a differential diagnosis is often difficult.

9 One should recognize the osseous changes characteristic of different stages of the disease, as shown in the roentgenogram.

10 Properly selected biopsy material is necessary to a dependable microscopic diagnosis. Errors may easily occur from ill chosen material.

11 The prognosis must be guarded, even after five years.

12 No specific treatment is known to be curative. Evidence seems to indicate that radical operation followed by irradiation offers the most hopeful prospect for life.

Dr. J. G. McFetridge, associate pathologist, gave valuable assistance in the preparation of this paper.

# CATGUT SUTURES AND LIGATURES

GREATER EFFICACY ACHIEVED THROUGH OBSERVANCE  
OF CERTAIN DETAILS

CYRUS F HORINE, M D

BALTIMORE

*'Good surgery is largely a matter of paying particular attention to little details'*—J M T Finney

Through the centuries it has been known that twisted fibers are strong even though individually their component parts resist little tension. Notwithstanding, little attention has been paid to the matter of the twist in catgut suture material as it may affect the tensile strength and absorption of the strand and the reliability of the knot. It may safely be admitted that some important and effective details in the practical use of catgut sutures and ligatures have been entirely overlooked. It is also to be admitted that surgeons have been rather careless in their use of catgut, and no doubt reckless with the truth in charging certain failures inadvertently to faulty material rather than to improper application.

The purpose of this article is to show how the twist and its variations can alter the tensile strength, the absorption of the strand and the reliability of knots. A preliminary presentation and review of the subject are given in another publication <sup>1</sup>

## EXPERIMENTAL DEMONSTRATION OF RELATION OF THE TWIST TO FRICTIONAL VALUES AND THE STRENGTH OF THE KNOT

In a simple experiment one may take a smooth, straight strand of catgut and carefully apply a large right hand throw (without acute bends or twists) to form a knot on the strand. When the two free ends are drawn taut, the loop gradually slides toward the right. There is little or no tendency for a loop made with a left hand throw to proceed to the right when the maneuver is carried out under similar conditions.

If one applies single right and left hand throws to a strand of non-boilable (hydrous) catgut and makes sufficient tension to break the knot, the right hand knot breaks first in the large majority of instances, as shown in the table. Various results are found when the test is applied to the anhydrous, or boilable, suture material. Variations of frictional

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<sup>1</sup> Horine, C F. Some Physical Factors Regarding Catgut Ligatures and Catgut Knots, to be published

values in the wet and dry strands have been clearly demonstrated in the valuable work reported recently by Taylor<sup>2</sup>

The tying of a knot, after all, is a matter of increasing the twist in the knot made with a right hand throw and decreasing the twist in the left hand knot, if the action is applied to the conventionally spun (clock-

*Tests on Strength of Knots \**

	00 Plain Catgut	No 1 Chromic, 10 to 20 Day
Straight pull tests for control	6 04†	12 09
Single right throw knots	3 23	6 80
Single left throw knots	3 63	8 60
Single right throw knots over glass rod	6 65	11 71
Single left throw knots over glass rod	5 64	10 35

\* The tests were made on catgut of three popular brands which had been bought on the open market. The results represent the averages (combined) of many hundred knots which had been broken. The proportional differences in the various knots compared well in the three different brands.

† All the figures represent pounds (1 lb = 453.59 Gm.)

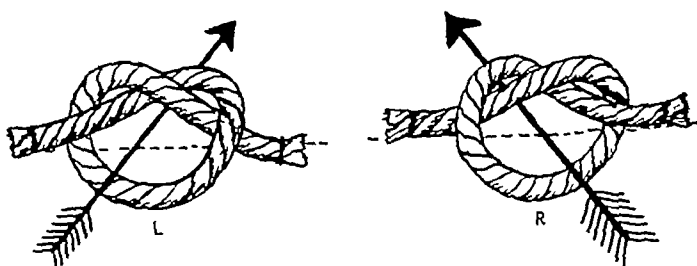


Fig 1—*L* shows a knot made by a left hand throw and *R* a knot made by a right hand throw. In *L* the horizontal axis forms an angle of approximately 135 degrees, as shown by the arrow, in *R* the horizontal axis forms an angle of approximately 45 degrees.

wise) hydrous, or nonboilable, material. However, other physical factors influence the degree and character of the torsion. The horizontal axis of the loop made with a right hand throw forms an angle of approximately 45 degrees, this angle decreases, as the loop is drawn to knot formation. The horizontal axis of the left hand loop forms an angle of approximately 135 degrees, this angle increases as the loop is drawn taut to form the knot (fig 1). Variations of the vertical axes of the loops are also to be noted.

Tension applied to the strands in the tightening of the loop to knot formation reduces the areas of frictional surfaces, and the knots break at the converging points of tension and friction. In the loop formed by a right hand throw there is a shearing of the strand quite transversely to its long dimension at the point of acute angulation. The lesser fric-

tion in the reduction of this loop to the "breaking knot" allows it to divide before the knot formed by the left hand throw in the test of the nonboilable, or hydrous catgut. The test of the right hand knot with its acute twist and subsequent fracture of the strands demonstrated the clinical phenomenon in which small bits of tissue are tied under apparent low tension. Too frequently the surgeon has quickly and erroneously concluded that this is due to defective material, when actual tests would have shown evidence of adequate tensile strength "on the straight pull."

When one makes similar experiments by tying single right and left hand throws over a glass rod approximately  $\frac{1}{4}$  inch (0.6 cm) in diameter, greater resistance to tension occurs in the right hand loop than in the left hand one, providing the various crossed strands are drawn in their respective normal planes and angles. Furthermore, considerably more tension is withstood in these tests than in the experiments previously described, this difference is shown in the accompanying table.

#### CLINICAL APPLICATION

The varied and controverted figures giving results of experiments on the use of catgut suture material are due to variations in method of preparation and in manner of experimentation as well as to carelessness or indifference in clinical procedure. While there is no intent in this paper to continue the old discussion of the relative merits of catgut as compared with other suture substances, it may be said that it is rather remarkable that through years of controversy catgut has retained much popularity and withstood many erroneous criticisms of bad results.

A fair appraisal of catgut as suture material will be made after the material has been tried under more exacting practical conditions. Only after such trial can answers be given to the following questions: What is the effect of torsional variations on tensile strength? What is the effect of torsional variations on the absorption of the strand? How should the torsional variations be respected in the methods of application of sutures and knots?

Adequate tensile strength is given in the materials now produced by the reliable manufacturers. In the ultimate analysis, tensile strength either on the straight pull or in knot tests is not the all important point to be considered in the case of nonboilable catgut suture or ligature. The relationship of moisture to torsional variations in the strand needs further consideration for the production of more reliable material. This will be discussed in a future communication.

In the simple tests of single right and left hand knots on the same strand, the strand torsion is increased in the knot formed by the right hand throw and decreased in that formed by the left hand throw. There-

fore it may be expected that the loss of twist in the left hand knot should cause it to break before the right hand knot. However, with the same amount of tension applied to the two, the lesser friction on the component parts of the knot made by the right hand throw allows that knot to be drawn tighter, resulting in shearing of the strand. Surgeons should be mindful of these facts when small bits of tissue are tied, especially when the smaller materials are being used.

One of the most important factors in the general problem is the relationship of the twist to the hydrolysis and the absorption of the strand. The loss of the twist exposes more surfaces of the material to the effect of tissue juices or other agents. This was demonstrated in a previous paper. Sutures and knots should be so placed that the twist and the tensile strength are preserved. The consensus is that the square, or reef, knot is the best one. According to Taylor, triple throw square knots, tied flat, are the most reliable for catgut. No doubt many clinical observations substantiate this opinion.

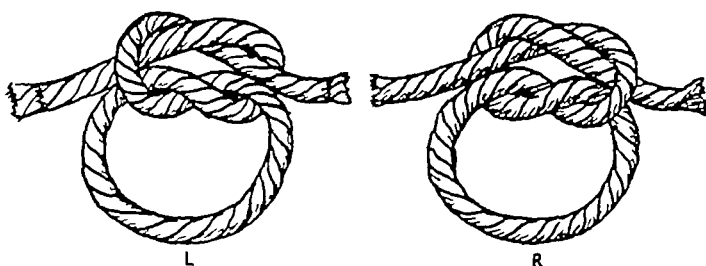


Fig 2—Right and left hand throws producing the two forms of square, or reef, knots. *L* shows a square knot which is formed by using the left hand throw (counterclockwise, opposite to the twist in the material) as the original throw, *R* shows the square knot which is made by using the right hand throw (clockwise, the same direction as the twist) as the original one. The knot shown in *R* is the best type, and it should be used consistently in catgut ligatures. Triple throws are more reliable, and in each type of knot the third throw should be the reverse of the throw forming the second loop.

*The Two Forms of Square Knots*—It is to be recognized that square, or reef, knots may be tied in two different forms with regard to the twist in the suture material. (1) In one form, the first throw of the knot is made to the right, the same direction as that of the twist in the conventionally spun material, while the second throw is made to the left, or counterclockwise, opposite to the direction of the twist, and if three throws are used, the third and final one should be applied in the right direction, (2) the second form is made by a reversal of the direction of all the throws just mentioned, a left hand throw being the initial one (fig 2).

The first form, originating with the right hand throw, is the more efficient, and particularly so in the use of hydrous, or nonboilable, material of variable water content, torsion and friction coefficient. While it must be remembered that in the tying of tissues of smaller diameters, the loop made by the right hand, or original, throw in this first type of knot breaks more easily (especially in the smaller sizes of catgut) than that made by the left throw, nevertheless by careful use the required tension is obtained with minimum injury to the strand. Increased torsion rather than separation of fibers results. Strangulation of tissues and shearing of the strand are effected under extreme tension. At the same time, insufficient tension within the suture loop and fracture of the strands occur if the strands are tied in exaggerated horizontal and angulated positions. This original throw of the knot is the most important one, and sufficient tension can be obtained within the suture loop when wet catgut is used, with less likelihood of "slipping" while the second throw is being applied. The clockwise rotation of the strand in the right hand simultaneous with the counterclockwise rotation of the strand in the left hand during the act of tying this particular throw, as pointed out in the other article, already mentioned, gives better results if the catgut is large and heavily saturated with moisture.

The second, or left hand (counterclockwise), throw completes the knot. The second loop is drawn flat with sufficient tension to lock the first one, and it is important, as already emphasized, that the strands should be drawn with the horizontal axis of the loop in an angle of approximately 135 degrees. In view of the fact that the direction of this throw is opposite to the torsional direction in the strand, one can close the loop with less tension by increasing the counterclockwise rotation of the crossed strands as they are being drawn taut. However, this is not to be recommended unless one is quite sure that the first throw has remained securely tied. Otherwise, if this unwound portion slides reversely through to become the areas adjacent to the knot, premature absorption occurs at these sites because of this loss of twist. Increased clockwise rotation of the strands during the act of tying a left hand throw increases the difficulty of tying the knot securely.

The third, and final, throw of the knot is carried out as described in the paragraph on the original right hand throw.

*Vertical and Horizontal Rotations of Knots and Sutures*—Surgeons, pathologists particularly, may have noted at autopsy that few square knots previously tied flat remain in this state. A partial explanation of this may be gained by consideration of the rotation of the knot proper and the rotation of the suspended loop portion of the suture. Pressure due to absorption of moisture causes the material to rotate in the counter-

clockwise direction in its attempt to straighten. A suspended loop of a suture under slight tension may not offer enough resistance to this pressure. If this occurs in a knot in which the original loop has been tied with a left hand throw, one can readily understand how the knot may slip from the flat condition (fig 3). The slipping is more apt to happen when the suspended loop of this particular knotted suture is so placed in the tissues that its horizontal axis is subjected to clockwise rotation. Likewise, counterclockwise axial rotation of the loop in a suture knotted by a right hand throw causes it to slip from the flat state.

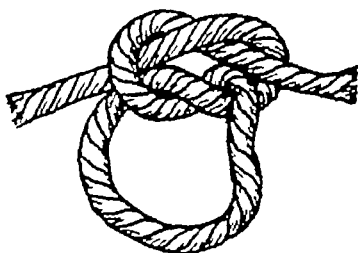


Fig 3—A left hand square knot, showing how the suspended loop in this type of knot can slip from the flat state. If tension or pull on the suspended loop is directed to the right, the knot easily slips from the flat condition. This is especially true of the left hand square knot because the absorption of moisture in the strand causes a counterclockwise rotation of the strand which, in turn, aids the rotation of this particular suspended loop.

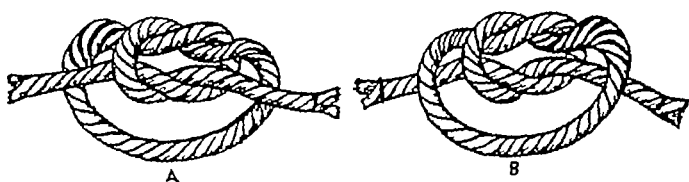


Fig 4—The austral, *A*, and boreal, *B*, rotation of a square knot on its suspended loop. Note in *B* the loss of twist to the right of the knot and the increase of twist to the left of the knot. In *A* there is an opposite effect on the twist in the material adjacent to the knot. This may be a partial explanation of the earlier dissolution of this particular portion of the ligature or suture, the loss of twist causes early absorption.

In this instance the strand retains its twist providing the knot remains tied, thus preventing rapid absorption in the area adjacent to the knot.

Even when the suspended loop of an interrupted suture is held in a fixed position, vertical rotations of its knot may take place. If they do, variations of strand torsion in the areas adjacent to the knot occur, regardless of the form of the knot. Boreal rotation of a right hand knot causes loss of torsion to the right of the knot and simultaneously produces an increase of torsion to the left of the knot. The reverse is true of the austral rotation of this knot (fig 4). In the left hand knot

boreal rotation causes a loss of twist to the right of the knot and an increase to the left of the knot. Austral rotation causes the reverse effects. These factors have a definite effect on the ultimate absorption of the strands in these particular areas.

#### COMMENT

Particular attention to the physical details mentioned in this paper will give better results in the use of continuous or interrupted catgut sutures. A continuous suture applied in the counterclockwise direction causes a loss of torsion, thereby imparting weakness to the strand. The interrupted suture will be discussed more fully in a future report.

#### SUMMARY AND CONCLUSIONS

Evidence to demonstrate the relation of torsional variations to tensile strength of knots in the conventionally spun nonboilable (hydrous) catgut suture material is presented. Right hand throws increase the twist in knot tying. Left hand throws decrease the twist. Single knots formed by right hand throws resist less tension than left hand knots when tissues of small diameters are tied, especially when smaller suture materials are used. Knots made by right hand throws resist more tension than those made by left throws when they are tied over tissues of larger diameters.

A knot made by a right hand throw may be tied more easily and more tightly if the clockwise torsion is increased during the act of tying the knot. If the twist is decreased during this procedure, it is more difficult to tie the knot and less tension is obtained within the suspended suture or ligature loop.

In this tying of a left throw knot it is easier to make the knot tight if the torsion of the strand is decreased. (This is not to be recommended as a routine procedure.) If the twist is increased when a left throw knot is being tied, it is more difficult to tie the knot securely.

The loss of twist in catgut suture material exposes more surfaces of the substance to the effect of the tissue juices, thus in turn hastens the absorption processes.

Tensile strength on straight pull tests is not the all-important matter. The material should be introduced into the wound in such a manner that the twist is preserved. This applies particularly to the tying of knots whatever their form may be.

There are two forms of square, or reef, knots. The right hand square knot originates with a throw made to the right, or in the same direction as that of the strand twist. The first throw in the left hand square knot is to the left, counterclockwise opposite to the direction of the strand torsion.



The right hand square knot is the better knot to use in catgut sutures or ligatures for the following reasons (1) The first, and most important, loop is tied with less tension and injury to the strand, (2) the knot is less apt to slip while the second throw is being tied, and (3) there is increased resistance in its suspended loop to the pressure caused by the absorption of moisture from the tissues, and therefore it is more likely to hold the flat state and preserve the twist in the areas adjacent to the knot

# SPONTANEOUS PNEUMOTHORAX FOLLOWING POSITIVE PRESSURE INTRATRACHEAL ANESTHESIA

REPORT OF A CASE

A F HEIDRICK, M D

W E ADAMS, M D

AND

H M LIVINGSTONE, M D

CHICAGO

Since the introduction of intratracheal anesthesia by Elsberg in 1909, this method of administration has become increasingly popular, especially in the field of thoracic surgery. Elsberg<sup>1</sup> mentioned the difficulties in determining the size of the catheter to be used in order to produce the desired distention of the lung. The determining factor is the freedom of outflow around the catheter. The importance of this is well illustrated in a case recently reported by Bradshaw.<sup>2</sup>

As to the exact amount of positive pressure which may be safely used, there seem to be marked differences in opinion. Coryllos,<sup>3</sup> as a result of his experimental work on human beings and dogs with the E and J resuscitator (using from plus 14 mm to minus 9 mm of mercury through the face mask), concluded that it was impossible to cause even the slightest trauma to the lungs with this pressure. He found that if a lung freshly removed from a dog was attached to the resuscitator it expanded and retracted rhythmically and became only moderately distended with a positive pressure of 15 mm of mercury, and that in order to produce rupture of the lung a positive pressure of from 52 to 58 mm of mercury was needed.

Macklin,<sup>4</sup> in his study on cats, found that positive intratracheal pressure could produce mediastinal emphysema, pneumothorax and even

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From the Department of Surgery of the University of Chicago

<sup>1</sup> Elsberg, C. A. Clinical Experiences with Intratracheal Insufflation (Meltzer), with Remarks upon the Method for Thoracic Surgery, *Ann Surg* 52 23 1910

<sup>2</sup> Bradshaw, H. H. Anesthesia for Intrathoracic Operations, *J Thoracic Surg* 8 293, 1939

<sup>3</sup> Coryllos, P. N. Mechanical Resuscitation in Advanced Forms of Asphyxia, *Surg, Gynec. & Obst.* 66 698, 1938

<sup>4</sup> Macklin, C. C. Pneumothorax with Massive Collapse from Experimental Local Overinflation of the Lung Substance, *Canad M A J* 36 414, 1937

subcutaneous emphysema The time required to produce these changes varied inversely with the pressure used With relatively small catheters, it was more difficult to produce a pneumothorax

Eisenbrey<sup>5</sup> showed that there is a wide variation between the pressure registered on the apparatus and that which actually exists in the trachea In 1 case when there was free outflow of air between the catheter and the trachea, a machine pressure of positive 20 mm of mercury gave an intratracheal pressure of 14 mm, at 30 mm of mercury the intratracheal pressure remained the same, and at 50 mm of machine pressure the intratracheal pressure was 22 mm Quite different were his results when the space between the catheter and the trachea was diminished With a machine pressure of 20 mm of mercury and an intratracheal pressure of 1 mm, slight constriction to the outflow raised the machine pressure to 24 mm of mercury and the intratracheal pressure to 5 mm Further constriction caused the pressures to rise to 30 and 14 mm of mercury respectively Eisenbrey further stressed the rapidity with which the intratracheal and pulmonary pressures rise to a dangerous degree with only a momentary stoppage of the outflow These facts have been substantiated more recently by Marcotte, Phillips and Adams<sup>6</sup> in studies of dogs and cats

Bradshaw reported a case of an 18 month old child who was to be operated on for a large intrathoracic neurofibroma Shortly after the intratracheal anesthesia was begun, subcutaneous emphysema of the neck was noticed, and an associated small pneumothorax on the right side was also present Uneventful mask anesthesia was given at a later date, and the operation was successfully performed With the second anesthesia a water valve to prevent too high an intratracheal pressure was introduced into the system Bradshaw's report suggests that the emphysema and pneumothorax were due to an inadequate outflow of gas around the intratracheal tube He mentioned the mechanical difficulties in administering intratracheal anesthesia to children, for a tube permitting the use of proper suction and an adequate administration of the anesthetic agent practically fills the trachea

In 1936, Stephens<sup>7</sup> reported 3 cases of contralateral pneumothorax complicating intrathoracic surgical treatment In his first case emphysema of the face and chest wall developed five hours after the operation Autopsy revealed complete collapse of both lungs as well as

5 Eisenbrey, A B Observations on the Use of Intratracheal Anesthesia in Experimental Work, *Surg, Gynec & Obst* 15 715, 1912

6 Marcotte, R J, Phillips, F J, Adams, W E, and Livingstone H Differential Intra-bronchial Pressures and Mediastinal Emphysema *J Thorac Surg* 9 346, 1940

7 Stephens, H B A Consideration of Contralateral Pneumothorax as a Complication of Intrathoracic Operations, *J Thoracic Surg* 5 471, 1936

a mediastinal emphysema. No actual tear in the mediastinal pleura or bronchial fistula could be found. No mention was made of the method by which the anesthetic agent was administered. In the second case positive pressure through the mask was used. No cutaneous emphysema existed, but autopsy showed contralateral pneumothorax. Again no tear in the mediastinum could be demonstrated. In his third case, the intratracheal tube was in place but the anesthetic mixture was given through the mask. During the operation the heart action ceased. Forced positive pressure was used for the remainder of the operation. The patient recovered after the obliteration of a spontaneous contralateral pneumothorax.

We wish to report a case of spontaneous pneumothorax following positive pressure intratracheal anesthesia administered during an operation on the stellate ganglion.

#### REPORT OF CASE

B. N., a 19 year old woman, was admitted to the hospital on June 14, 1938, because of pain in the third finger of the right hand following an orthopedic operation in March 1937. At the age of 4 years the patient had a right hemiparesis and aphasia which developed suddenly a few days after a tonsillectomy. The right facial weakness and aphasia gradually disappeared, but severe paresis of the right arm and moderate paresis of the right leg persisted. In 1936 and 1937 she had a series of operations on the right forearm. After the operation in March 1937 she had continuous pain in the right middle finger which was exacerbated by moving the second, third or fourth finger.

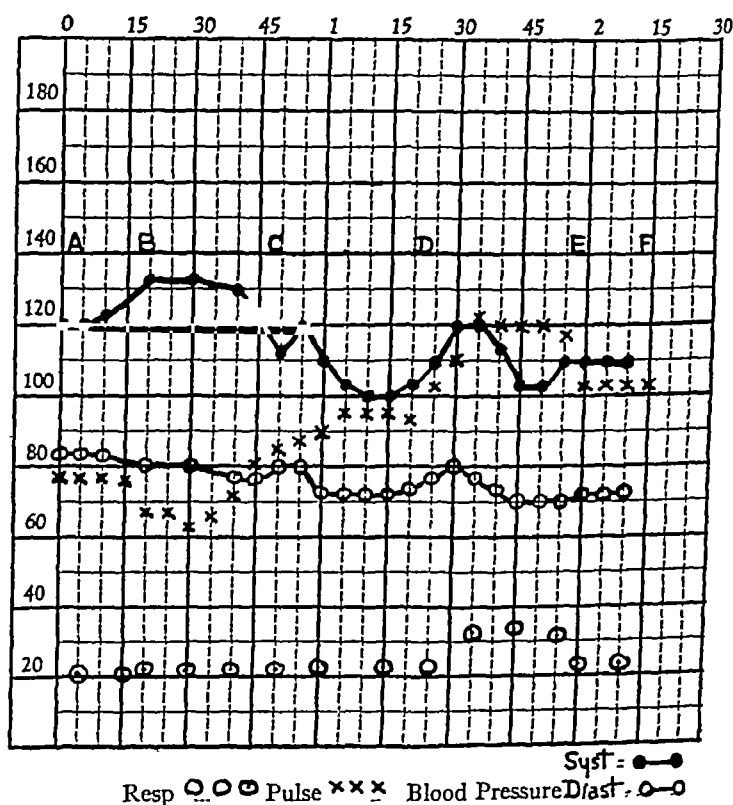
*Physical Examination*—The patient was a slightly obese woman of 19 years. General examination revealed a condition essentially normal except for the right arm. This arm was atrophic and spastic, carried in a flexed position with the hand held in the same straight line (owing to a previous bone graft operation), and the fingers were firmly flexed into the palm. There was marked resistance to passive movement.

*Treatment*—The patient received infiltration of procaine hydrochloride into the hand, injection into the median nerve at the elbow and paravertebral injection in the right upper thoracic region on different occasions. All of these injections relieved the pain in the finger for a short time.

*Operation*—On June 21 a preganglionic sympathectomy (right side) in the upper part of the thoracic region was done. The anesthesia was produced by intratracheal administration of ether and oxygen after an ethylene-oxygen induction. A no. 8 Magill tube was introduced through the nose and directed into the larynx under direct vision. Intubation was easily accomplished with no evidence of injury to the respiratory tract. There was no mucus in the throat. A no. 16 Foregger bag with an exhalation valve was attached to the intratracheal tube by a 24 inch small rubber tubing. Ether vapor and oxygen were delivered into this bag. Anesthesia was maintained by the semiopen method with the exhaling valve partly open. Some manual pressure was used on the bag during the operation when a hole was made in the pleura and at a positive pressure of 12 mm. of mercury (as measured at the head of the machine) oxygen was given for three minutes by

attaching the bag to the anesthetic machine just before closure of the chest to secure lung expansion. The exhaling valve remained half open during this time, the right lung was seen to expand well. Throughout the entire operation blood pressure, pulse and respiration showed no marked variations, as is shown in the accompanying chart.

*Postoperative Course*—The patient complained of difficulty in breathing as soon as she regained consciousness, but she did not at that time appear dyspneic, and her general condition was good. At 3 a. m. the following day (fourteen hours postoperatively) marked subcutaneous emphysema was noted over the right side of the head and neck, extending below the scapula and over the right temple. The patient was definitely dyspneic. A roentgenogram taken at that time showed a total



Data on the operation which was followed by spontaneous pneumothorax. The abbreviations represent A, beginning of anesthesia, B, intratracheal intubation, C, beginning of operation, D, small hole in pleura, positive pressure, E, beginning of closure, positive pressure, F, completion of operation.

pneumothorax with complete collapse of the left lung, but no shift of the mediastinum. Four hundred cubic centimeters of air was withdrawn from the left pleural cavity, which resulted in relief of the dyspnea. The next day air was again aspirated at intervals from the left pleural cavity, and the symptoms were again relieved. On the second postoperative day (June 23) the emphysema was less marked, and there was no difficulty in breathing. The subsequent convalescence was uneventful. There was little febrile reaction. On June 28 roentgenogram of the chest were normal. On July 1 the patient was discharged to the outpatient and the physical therapy departments for further treatment of her much improved hand and arm, which were painless after the operation.

## SUMMARY

It has been demonstrated both experimentally and clinically that excessive positive pressure used in producing anesthesia may result in serious pulmonary complications. The exact amount of positive pressure which can be safely used is not certain. That the machine pressure is no accurate index of the intratracheal and intrapulmonary pressure was shown experimentally by Eisenbrey in 1912 and more recently by Marcotte, Phillips and Adams. The freedom of outflow around the intratracheal catheter seems to be one of the most important factors in the determination of the amount of positive pressure existing in the tracheobronchial air passages. Bradshaw reported a case in which emphysema and pneumothorax complicated intratracheal anesthesia when no operation was performed. Stephens reported a case of generalized emphysema and contralateral pneumothorax occurring after an intrathoracic operation. No mention was made by Stephens of the type of anesthesia used.

One neurosurgical case in which the intratracheal anesthesia was seemingly uneventful but in which spontaneous contralateral pneumothorax developed postoperatively is reported. In this case relatively low positive pressure was used.

# PROBLEM OF CARCINOMA OF THE BREAST

## RADICAL MASTECTOMY IN NINETY CASES

C A KUNATH, MD

SAN ANGELO, TEXAS

The following report represents a study of the patients with malignant tumor of the breast admitted to the University of Iowa Hospitals during a five year period (1927 to 1932), with an analysis of the results five to ten years after radical mastectomy. In this respect it is essentially another report of so-called five and ten year cures, however, it is my endeavor to present a somewhat broader aspect of the subject. Although the percentage of operative "cures" of carcinoma of the breast has been steadily increasing during recent years, there are still certain features which indicate that a final solution to the problem has not been reached. It is hoped to emphasize certain factors which may be of assistance in improving the results.

The better known clinics throughout the United States are now reporting five year "cures" in from 30 to 60 per cent of their cases, and the general tone of the various reports tends to give rise to a feeling of optimism. Some would explain this progress on the basis of improvements in operative technic, others, on the basis of recent advances in the technic of irradiation. A third explanation is that patients are now being seen earlier in the course of the disease and therefore respond more favorably to surgical treatment. Encouraging as these figures may be, one must not lose sight of the fact that they are based only on operable tumors and that they leave untold the fate of a vast number of patients whose lesions are inoperable when first seen by the surgeon and are therefore largely responsible for the high death rate from the disease.

Of the patients studied in the present series, 38 per cent were considered inoperable when first seen. The follow-up study of the surgically treated patients showed five year survivals in 50.5 per cent of instances, a figure which compares favorably with those from other, similar clinics. But when one considers the number of survivals in respect to the total number of patients seen, both operable and inoperable, the percentage of five year survivals drops to about 30 per cent. This is the figure that has real significance when one considers the disease in its entire scope.

In 1927, Daland<sup>1</sup> published the results of a study of 100 untreated patients with mammary carcinoma who had either refused operation or

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From the Department of Surgery, University Hospitals, Iowa City

<sup>1</sup> Daland, E. M. Untreated Cancer of the Breast, Surg., Gynec. & Obst.

presented evidence of inoperability when first seen. The average duration of life for these patients from the time of the first symptoms was forty and five-tenths months. Twenty-six per cent of the group lived five years without any treatment, 5 per cent lived ten years. Two of the patients lived thirteen years. From the reports of other workers who have followed untreated patients it would appear that the average life expectancy from the first symptoms of carcinoma of the breast is in the neighborhood of three years. With these facts in mind it becomes evident that the significance of postoperative "five year cures" may be less than has been considered.

Finally I have shared a growing conviction that the term "cure" is not a good one to use in speaking of patients recovering from radical mastectomy for cancer of the breast. There are numerous instances in the literature of metastases appearing fifteen and twenty years after

TABLE 1—*Classification of Patients with Mammary Carcinoma*

Operable	91
Radical mastectomy done	90
Operation refused	1
Inoperable on admission	56
Treated by irradiation only	41
Treated by simple mastectomy	15
Primarily treated elsewhere entered with metastases or recurrence	18
Carcinoma of male breast*	3
	<hr/> 168

\* Carcinoma of the male breast presents a somewhat different problem and these 3 cases are therefore included in a separate report (Carcinoma of the Male Breast J. Iowa M. Soc. 28: 10, 1935).

operation, and 1 case has been reported in which an interval of forty-three years occurred between radical mastectomy and the appearance of metastases. Carcinoma of the breast is notorious in this respect, and there is probably no time in the patient's postoperative life when she may consider herself absolutely free of the possibility of metastases. It would appear, therefore, that the term "survival" is much more appropriate than "cure" in referring to patients who remain in good health for a number of years after operation, and this term will be used henceforth in this report.

During the five year period between July 1, 1927 and July 1, 1932, there were 168 patients with carcinoma of the breast admitted to the University of Iowa Hospitals. These patients are classified in table 1.

The criteria of operability in this clinic correspond closely to those used elsewhere. Radical mastectomy was not carried out when the following conditions presented themselves:

1. Demonstrable metastases to the skeletal system or other remote organs.



- 2 Demonstrable involvement of the supraclavicular lymph nodes
- 3 Far advanced ulcerative conditions or marked fixation to the chest wall
- 4 Very poor general condition or associated lesions making the prognosis for life limited
- 5 Rapidly growing so-called "acute carcinoma" arising in the lactating breast or during pregnancy

Table 2 shows the operability rate as recorded by years. This analysis was also carried through a subsequent five year period (from 1932 to 1937) in order to note any improvement which might have occurred in this phase of the problem. It will be seen that so far as this particular clinic is concerned little progress has been made in regard to the percentage of operable patients reporting for treatment.

TABLE 2—Operability Rate

1927	61.6%	1932	67.9%
1928	50.0%	1933	83.6%
1929	71.4%	1934	56.2%
1930	70.6%	1935	78.0%
1931	68.7%	1936	65.7%

#### ANALYSIS OF NINETY CONSECUTIVE RADICAL MASTECTOMIES

The cases of the 90 surgically treated patients have been carefully analyzed and present an interesting cross section of the problem of mammary carcinoma in general. The salient features of this analysis are presented in the following sections.

*Vital Statistics*—The average age for the group was 52.5 years, the extremes being 74 years and 25 years. There were 17 patients, or 18.8 per cent, under 40 years of age. The time that elapsed between the first symptom of trouble with the breast and the first visit to the physician varied from one day to twenty years. There was usually a delay of from six to eighteen months.

*Causation*—There was a history of preceding trauma in only 10 cases, or 11 per cent. Two patients stated that they had had a benign tumor removed from the breast four and five years respectively prior to admission. Ten patients stated that they had had a "caked breast" or an abscess of the breast in the past, again 11 per cent of the entire group. In other words, the majority of patients gave nothing in their history to suggest a possible cause, and this corresponds rather closely with the observation of most other workers on the subject. On the other hand, some observers believe that lymph stasis is a most important factor

in the development of malignant tumor of the breast Trout<sup>2</sup> was able by careful questioning to elicit a history of some type of dysfunction of the breast in 88 per cent of cases

*Symptoms*—The first symptom noted was usually a mass in the breast, discovered by the patient this occurred in 84.4 per cent of cases Pain was the symptom next in frequency, being the first symptom in about 8 per cent of the series Most of the standard textbooks have minimized the incidence of pain in carcinoma of the breast, stating that the lesion is essentially painless This is probably true in the early stages, but 39 per cent of the patients in our series were found to have had either pain or tenderness at sometime during the course of the disease Discharge from the nipple was noted in only 12 cases, or 13.3 per cent The bloody discharge mentioned in textbook descriptions was noted only 4 times In 1 case the first symptom discovered was

TABLE 3—*Distribution of Lesions*

Upper half		61
Upper lateral quadrant	41	
Upper medial quadrant	12	
Both upper quadrants	8	
Lower half		20
Lower lateral quadrant	9	
Lower medial quadrant	6	
Both lower quadrants	5	
Lateral half		51
Medial half		20
Directly beneath nipple		1
Entire breast		1
Axillary tail		1

retraction of a nipple In another case the first complaint was of neuritic pain down the arm

*Physical Findings*—Many authors have observed that carcinoma of the breast is most frequently located in the upper and lateral quadrants of the breast, and this has proved to be an interesting subject for speculation In the present series of cases the lesions were located as shown in table 3 It will be seen that there were three times as many tumors in the upper lateral quadrant as in its nearest competitor, the upper medial quadrant There were 61 lesions in the upper half of the breast as compared to 20 in the lower half nearly three times as many There were nearly three times as many lesions in the lateral half of the breast as in the medial half The usual explanation of this overwhelming preponderance of tumors in the upper half of the breast is that lymphatic drainage is poor because of inadequate support of the breast The data that have been accumulated are so consistent that there would seem to

<sup>2</sup> Trout, H. H. Carcinoma of the Breast. A Study in Etiology and Prognosis. *Am J Surg* 24:258, 1934.

be ample grounds for advising some type of uplift brassiere for proper support of the breast

Fixation to the skin, including the nipple, was noted clinically in 48 of the 90 cases and served to emphasize again that the familiar orange peel appearance of the skin is a frequent and early finding. Some degree of ulceration of the skin was present in 7 cases.

*Axillary Metastases*—The presence of axillary metastases, although not considered a sign of inoperability, is of first importance from the standpoint of prognosis. In this series of radical mastectomies microscopic examination revealed the presence of metastases to the axillary lymph nodes in 55.5 per cent of cases.

Overholt and Eckerson<sup>3</sup> have pointed out that the clinical diagnosis of axillary metastases is often incorrect, since, on the one hand, the nodes may be inaccessible to the palpating finger and, on the other hand, a certain part of the enlargement of the lymph nodes may be on the basis of simple chronic hyperplastic lymphadenitis. Investigation of this point in the present series showed numerous errors in both directions. There were 41 cases in which a clinical diagnosis of axillary metastases was made. In only 30 of these were metastases demonstrated on histologic section, an error of 27 per cent. There were 49 cases in which no nodes were palpated clinically. In 20 of these metastases were demonstrable on histologic section, an error of 41 per cent. Thus, the total diagnostic error was found to be 34 per cent.

Similarly, it was found that the clinical diagnosis of involvement of the skin was often in error. Of the 48 cases in which there was clinical involvement of the overlying skin, sections showed actual invasion of the skin in only 19, or 40 per cent. In the other cases the cutaneous condition was probably simple lymphedema or was due to traction on the skin from deeper structures.

*Operative Technic*—The extent of the dissection in radical mastectomy has become pretty well standardized since Halsted described his technic in 1888, and the chief differences of opinion today center around such details as the amount of skin to be removed, the type of suture material to use and the closure of the defect by primary skin approximation or by Thiersch graft. In the present series of cases an attempt was made to preserve skin wherever feasible and to approximate the edges of the skin primarily in every case if possible. As a result, primary skin graft was carried out only 11 times, an incidence of 12.2 per cent.

*Postoperative Mortality and Morbidity*—In this group of 90 consecutive radical mastectomies there was not a single operative death. The earliest recorded death occurred three months after operation and more than two months after the patient's discharge from the hospital.

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<sup>3</sup> Overholt, R. H., and Eckerson, E. B. The Treatment of Cancer of the Breast and the Results of Operation, New England J. Med. **211**:703, 1934.

Among the postoperative complications, infection led the list, and there were 27 patients or 30 per cent, who had some degree of sloughing of the cutaneous margins or infection in their wounds. Nine of these defects were considered extensive enough to require secondary skin grafting. The next most common postoperative complication was lymphedema of the arm, which occurred in 10 per cent of the cases. Thrombophlebitis of the axillary vein occurred in 2 cases. There was 1 instance of pulmonary infarct and 1 case in which the postoperative course was complicated by erysipelas of the wound. The average period of hospitalization was twenty-two days, the extremes being six days and ninety-two days.

TABLE 4—*Status of Patients Five to Ten Years After Operation*

Patients living	32
Living and in good health	31
Living with local recurrence	0
Living with metastases	1
Patients dead	58
Died of carcinoma of breast	52
Died of other cause*	6
	90

\* Cancer of stomach 2 cancer of cervix 1 diabetes 1 cerebral hemorrhage 1 psoriasis and general debility 1

TABLE 5—*Percentage of Survivals for Each Year After Operation*

1 year survivals (82 out of a possible 90)	91.0%
2 year survivals (68 out of a possible 90)	75.5%
3 year survivals (59 out of a possible 89)	66.3%
4 year survivals (50 out of a possible 87)	57.6%
5 year survivals (43 out of a possible 85)	50.5%
6 year survivals (32 out of a possible 77)	41.6%
7 year survivals (17 out of a possible 58)	29.3%
8 year survivals (11 out of a possible 40)	27.5%
9 year survivals (4 out of a possible 17)	23.5%
10 year survivals (2 out of a possible 7)	28.6%

#### FOLLOW-UP RESULTS

I was especially fortunate in obtaining a follow-up report in 100 per cent of cases in this series. The lapse of time since operation varied from five to ten years. The status of the group at the time the survey was made is shown in table 4.

Table 5 shows the percentage of survivals for each year following operation. The term "survival" is used only for patients in good health without evidence of metastases or recurrence.

The incidence of local recurrence in the series was 18.9 per cent. The time of appearance varied from four months to five years post-operatively, the average interval being eighteen and three-tenths months.

The group was not particularly suited for the study of metastases, since most of the patients died at home, and postmortem examinations were not made. However, from the evidence at hand, the following incidence of metastatic lesions was ascertained: skeletal system, 18 (spine, 8, pelvis, 7, ribs, 3, femur, 3, skull, 2, clavicle, 1, sternum, 1), lungs and pleura, 16, liver, 8, peritoneum, 4, opposite breast, 4, mediastinal lymph nodes, 3, skin, 2, and brain, scalp, pancreas, adrenals, larynx and pericardium, 1 each.

Warren<sup>4</sup> in a study of 162 cases of cancer of the breast in which autopsy was done observed only 8 in which there were no metastatic lesions. He stated that practically every organ in the body has been noted as a site of metastases, and in his study the eye, the middle ear, the nasopharynx and the pineal gland were the only tissues to be spared.

#### COMMENT ON RESULTS

It will be noted from table 5 that the percentage of five year survivals was 50.5, a figure which compares favorably with those reported from similar clinics. Hutchinson<sup>5</sup> in an extensive analysis of the world literature in 1936 found that five year survivals averaged 28.1 per cent with operation alone and 40.9 per cent with operation plus irradiation.

The death rate was highest in the first few years after operation and tended to level off after the seventh year. In other words, for every year the patient survives after operation the prognosis for cure becomes better.

The incidence of local recurrences (18.9 per cent) may seem unduly high and caused my associates and me to consider the advisability of wider cutaneous excision. After Halsted devised his "complete" operation in 1888, he reported that he had reduced the incidence of local recurrence from over 60 per cent to 6 per cent.<sup>6</sup> However, at that time the longest postoperative duration of life in any of his patients was about three years. Subsequent reports by Halsted put the figure at 9 per cent, then 27.1 per cent, then 31.9 per cent. Lewis and Rienhoff,<sup>7</sup> in an analysis of the cases from the Johns Hopkins Hospital in 1932, reported local recurrences in a range from 32.2 to 15.2 per cent of cases. These authors made a strong plea for wide cutaneous excision and

4 Warren, S., and Witham, E. M. Studies on Tumor Metastases. The Distribution of Metastases in Cancer of the Breast, Surg., Gynec. & Obst. **57** 81, 1933.

5 Hutchinson, R. G. The Value of Radiation Therapy in the Treatment of Carcinoma of the Breast, Surg., Gynec. & Obst. **62** 653, 1936.

6 Halsted, W. S. Surgical Papers of William Stewart Halsted, Baltimore, Johns Hopkins Press, 1924, vol. 2.

7 Lewis, D., and Rienhoff, W. F. A Study of the Results of Operations for the Cure of Cancer of the Breast, Ann. Surg. **95** 336, 1932.

primary Thiersch graft, stating that by this procedure alone is it possible to reduce local recurrences to a minimum

Although these views reflect the teaching of Halsted, who may properly be called the father of modern breast surgery, there are enough accumulated statistics to lend considerable doubt as to their practicability. In the first place, the percentage of recurrences reported by these authors is not as low as those of some clinics where closure of the wound is carried out primarily. Lee<sup>8</sup> in analyzing the cases from the Memorial Hospital, New York, found local recurrences in only 13 per cent, and nearly all of the operative wounds were closed primarily without grafting. In the present series of cases primary skin grafting was carried out eleven times owing to extensive ulceration necessitating wide excision of skin. It is probably true that these patients represent a group in a more advanced stage of the disease and therefore a less favorable prognosis. Be this as it may, the fact remains that there were local recurrences in 47.3 per cent of this group as compared to 17.7 per cent in which primary closure was done.

Secondly, the postoperative mortality is appreciably higher where the Halsted Thiersch graft procedure is employed, and in the series reported by Lewis and Reinhoff it was 6.4 per cent.

Finally, one must face the fact that the patient with carcinoma of the breast does not die from local recurrence but from metastases, and often these are far distant from the site of the primary lesion.

It is the opinion of this clinic, therefore, that a point has been reached where one can expect little improvement in results from increasing the magnitude of the operation. This viewpoint has been admirably expressed by Mathews,<sup>9</sup> who stated "We may extend the area of skin removal indefinitely but what is gained when the site of the recurrence is within the chest?"

#### FACTORS IN PROGNOSIS

A great deal of insight into the problem of carcinoma of the breast can be gained by consideration of the various factors influencing prognosis. The factors which have been mentioned in the past are discussed briefly in connection with the present series of cases.

1 *Age*—The influence of age is well known and follows the generally accepted fact that any malignant growth occurring in a young person is apt to be much more rapidly growing and earlier to metastasize. In the present series of 90 cases there were 17 patients under 40 years of age with five years survivals in only 5 instances, or 29 per cent.

<sup>8</sup> Lee, B. J. End Results in the Treatment of Cancer of the Breast by Radical Surgery Combined with Preoperative and Postoperative Irradiation. *Am J Surg* 20: 405, 1933.

<sup>9</sup> Mathews, F. S. Results of Operative Treatment of Cancer of the Breast. *Ann Surg* 96: 871, 1932.

2 *Lactation* — Although there has never been any conclusive proof that cancer occurs more frequently in breasts which have lactated, some workers believe that there has been some type of dysfunction in the breast in practically every case of malignant disease. On the other hand it is rather definitely established that carcinoma arising in an actively lactating breast or during pregnancy is an exceedingly dangerous lesion. Five year survivals in such cases are practically nonexistent. Trout<sup>10</sup> warned women never to become pregnant after having had an operation for cancer of the breast. Of 15 collected cases in which postoperative pregnancy occurred, cancer developed in the opposite breast in 13 or 87 per cent, and all 13 patients died promptly of carcinoma. Although there are no such cases in the present series, I have observed several during the past few years and have learned to consider such lesions as among the most rapidly growing and progressively fatal of all malignant growths. The practice of producing artificial menopause in the treatment of malignant mammary disease is becoming generally adopted throughout the United States and is logically based on the known inter-relation between the breast and the ovaries. The factor of lactation in prognosis can probably be summed up by saying that if it is coexistent with a malignant tumor of the breast the prognosis is made much more unfavorable, while previous lactations exert a detrimental effect only so far as they have left residual dysfunction, irregularity or inflammatory episodes.

3 *Duration of Symptoms Before Operation* — For evaluation of the importance of this factor, see section 4.

4 *Rate of Growth* — Greenough and Taylor<sup>11</sup> stated that the pre-operative duration of the tumor, as recorded by the patient, is of very little value in prognosis. Lewis and Rienhoff<sup>7</sup> also found this factor to have very little significance in regard to longevity after operation. My own observations are in agreement with these views, and in the present series some of the patients who had delayed longest before consulting a physician are among those who have survived for five years. Since there is such a great variation in the rate of growth of carcinoma of the breast it would appear that this factor is the important one to consider, rather than the actual time that the tumor has been present. One can probably conclude, therefore, that while the duration of symptoms is of minor importance, the rate of growth is probably among the most important of prognostic factors.

5 *Size of Mass* — An analysis of this point failed to reveal that a large tumor carries any more serious a prognosis than does a small one.

10 Trout, H. H. *Carcinoma of the Breast*, Surg., Gynec. & Obst. **60** 476, 1935.

11 Greenough, R. B., and Taylor, G. W. *Cancer of the Breast. End Results*, New England J. Med. **210** 831, 1934.

Here again the significant feature is not the size of the mass but the rate of growth and the extent of the disease at the time of operation

6 *Location of Mass*—Lee<sup>8</sup> has stated that tumors of the upper medial quadrant of the breast carry the best prognosis, while those of the lower half and upper central position carry the most unfavorable. I was unable to verify this conclusion in the present series of cases and found the percentage of five year survivals to be practically the same for each quadrant of the breast examined

7 *Axillary Metastases*—The importance of axillary metastases in prognosis is probably the best accepted of any of the various factors that have been discussed. This point has been analyzed by practically all workers on the subject, and the conclusions are quite consistent throughout. Hutchinson,<sup>5</sup> in his review of the published statistics in 1936, found the average percentage of five year survivals to be 35 in cases in which there were axillary metastases and 71.3 per cent in cases in which no axillary metastases were present—a difference of 36.3 per cent. An analysis of the present series of cases shows figures which are very similar

Total 90 cases	50.5% five year survivals
40 cases without axillary metastases	72.5% five year survivals
50 cases with axillary metastases	30.0% five year survivals
Difference	42.5%

An analysis of the cases in which death occurred showed that the average duration of life in the patients with axillary metastases was two and sixty-seven hundredths years, while those without axillary metastases lived an average of four and seventeen hundredths years, or nearly twice as long.

Doubtless if it were possible to subdivide the patients with axillary metastases still further—as to the portion of the axilla involved, size of the nodes, and degree of fixation—one could gain even greater prognostic information. Trout<sup>10</sup> has mentioned that one large axillary node gives a much better prognosis than do numerous shotlike glands, and it has been common observation that when the extremely apical glands of the axilla are involved the prognosis is made definitely less favorable. In the experience of Bloodgood<sup>12</sup> the five year survivals will average about 70 per cent when the axillary glands are not involved. When these glands are involved the figure drops to 25, 20 and 10 per cent depending on whether the basal, the medial or the apical glands are involved and on the skill of the operator.

8 *Involvement of Skin*—This feature was analyzed without finding anything of prognostic significance. The patients with involvement of the

<sup>12</sup> Bloodgood J. C. Biopsy in Breast Lesions. Ann Surg 102:239 1935



skin lived just as long as the others, and there were 57.9 per cent of five year survivals in this group as compared to 50.5 per cent for the entire series.

9 *Histologic Grading*—Numerical grading was not carried out in this series of malignant tumors, but some workers feel that this procedure is probably the best index of prognosis that has been discovered. The modified Broder's classification developed by Greenough<sup>13</sup> at the Massachusetts General Hospital proved to be a valuable prognostic index in his hands, nevertheless, he stated the belief that it should always be considered in connection with the extent of the disease and other factors. Lewis and Rienhoff also expressed doubt whether prognosis should be based on the histologic picture alone. Trout<sup>10</sup> stated that the histologic index is not nearly as important or as accurate as a well considered clinical index.

Among the various clinical indexes which have been formulated, probably the most popular is that of Lee and Stubenbord<sup>14</sup>. These authors have taken into account four factors—age, lactation, rate of growth and extent of the disease, which, as may be recalled, are the most significant of the several factors which have just been discussed. Each of these factors is evaluated as increasingly significant in the order named, and they are further evaluated by gradation factors within themselves. Although clinical application of the formula may appear somewhat laborious, it serves to emphasize the relative importance of the various factors to be considered in prognosis.

#### THE PROBLEM FOR THE FUTURE

The importance of any survey of postoperative results lies in the opportunity it affords for looking into the future. What are the ways and means at hand for improving the results? It is already fairly evident that no drastic improvement can be made from the standpoint of operative technic. The various electrical units and the hot loop knife have many advocates and probably offer certain advantages in all surgical procedures on malignant tumors. As concerns the many incisions that have been proposed, it would seem that this is a matter to be individualized for each patient according to the location of the mass in the breast and the extent of involvement. There is probably no one incision that can be used successfully in every case, and the extent of the subsequent dissection varies little with any of those proposed. The views of this clinic in regard to extensive excision of skin and primary skin grafting

13 Greenough, R. B. Five Year Cures of Cancer of the Breast at the Massachusetts General Hospital, Surg., Gynec. & Obst. 58:437, 1934.

14 Lee, B. J., and Stubenbord, J. G. A Clinical Index of Malignancy for Carcinoma of the Breast, Surg., Gynec. & Obst. 47:812, 1928.

have already been expressed. Our experience has led my associates and me to agree with Mathews that the percentage of cures of carcinoma of the breast is not proportionate to the time devoted to the operation or to the amount of skin removed. The important thing would appear to be a reasonable type of radical mastectomy carried out while the lesion is still confined to the breast.

With this objective in mind at least three avenues of approach to the problem are suggested:

- 1 Prophylaxis
- 2 Education of the laity
- 3 Irradiation

1 *Prophylaxis*—The relation of cancer of the breast to previous dysfunction has already been mentioned under the discussion of causation. The occurrence of two thirds of all mammary cancers in the upper half of the breast cannot be ignored and argues strongly for proper support of the breasts as an important prophylactic measure. The relation of pelvic disorders, the proper care of the breasts during pregnancy and lactation and the effect of subsequent pregnancies after removal of a carcinoma of the breast have all been admirably brought to light by Trout<sup>10</sup> and deserve the attention of every practicing physician.

2 *Education of the Laity*—This approach to the subject is based on the firm knowledge that earlier recognition of the disease is the best means at hand of improving the results. It is highly significant that radical mastectomy in this clinic when carried out before the axillary glands were involved offered a five year survival in 72.5 per cent of the cases. The crux of the problem lies in obtaining a reduction in the large number of tumors which are inoperable when first seen by the surgeon. The American Society for the Control of Cancer is already making strides in this field in educating the laity as to the first signs of the disease and the serious implications that may attend any lump in the breast. That this propaganda is actually producing results has already been shown in some clinics if not in this one. At the Mayo Clinic the operability rate rose from 55 per cent in 1926 to 73 per cent in 1936 and other clinics are reporting similar increases.

3 *Irradiation*—It seems likely that the radiologist will play an even more important role in the future treatment of malignant disease of the breast than he has in the past. Definite advances are constantly being made in this field by the use of higher voltages and by newer methods of application. The principle of preoperative irradiation appears to be gaining favor steadily in spite of the disagreements about it a few years ago.

In most of the cases reported in the present study radiation was given after mastectomy but in none of them was preoperative irradiation

carried out, because this procedure was not instituted at the University Hospitals until 1932. Since 1932 it has become a routine procedure, but there has not yet been sufficient time to permit evaluation of the results in terms of five year survivals. Consequently, the experience of this clinic in this regard is still in terms of impressions rather than actual statistics. The reports from other clinics concerning preoperative irradiation are for the most part encouraging, and as advances are being made in the field of roentgen therapy the use of irradiation may become an even more valuable adjunct to surgical treatment than it is at present.

#### SUMMARY

Another series of operative cases of carcinoma of the breast is added to the literature for the statistical value it may afford. This report represents an analysis of the results from five to ten years after radical mastectomy, a follow-up report having been obtained in 100 per cent of the cases.

The various factors in prognosis are discussed in regard to their relative importance, the most significant ones being the presence or absence of axillary metastases, the rate of growth, the coexistence of pregnancy or lactation and the age of the patient.

It is suggested that the term "survival" be substituted for "cure" in referring to patients who live for varying periods after operative treatment.

An attempt has been made to view the problem of cancer of the breast in its entirety rather than as a survey of a group of operative cases. The methods of improving the results become more clearly defined when viewed from this standpoint and seem to be chiefly along the lines of prophylaxis and earlier recognition of the disease.

The differences of opinion that exist in regard to operative technic are discussed, and the conclusion is reached that no improvement in end results can be hoped for by making the operation more radical. Rather, the goal should be a reasonably radical mastectomy performed while the malignant growth is still confined to the breast.

# EFFECTS OF LOCAL REACTION IN SPONTANEOUS TUMORS OF ANIMALS AND HUMAN BEINGS

FREDERICK M. ALLEN, M.D.

NEW YORK

It has been shown elsewhere<sup>1</sup> that temporary asphyxia produced by local ligation damages tumors selectively, in such a manner as to cause extensive and sometimes complete necrosis of the tumor while the normal tissues are unharmed except for transitory inflammation. These results (with transplanted tumors of rats and mice) were substantially duplicated with the chicken sarcoma,<sup>2</sup> which is composed of autogenous cells, but the persistence of the chemical excitant was assumed to be responsible for the trivial number of actual cures in proportion to recurrences and deaths. It was obviously desirable to extend the trials of asphyxia to tumors native to the mammalian body. Circumstances unfortunately did not warrant undertaking the chemical production of tumors with tar derivatives. A number of rat and mouse tumors were obtained by special arrangements with large dealers.

## 1. RAT FIBROMA

This is a common benign growth which develops slowly to huge size, sometimes being as large as the rat's body. It also springs usually from a rather narrow pedicle or is sufficiently separate from the body to permit ligation. As it is composed essentially of a low order of tissue, namely, tough, mature white fibrous tissue, it might be expected theoretically to survive prolonged asphyxia. Three examples of different sizes were obtained, and all were found to break down with trivial ligations of one or two hours. This result was not due to thrombosis in the rather scanty supply of main blood vessels, as was shown by the finding of liquid blood and small hemorrhages afterward. The process rather begins as an extensive central necrosis which spreads rapidly to the periphery. In the case of large tumors the shock and gangrene kill the rat. The endurance of temporary lack of circulation is therefore vastly less in a fibrous tumor than in normal tissues of a similar order, such as connective tissue or bone.

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<sup>1</sup> Allen, F. M. To be published.

<sup>2</sup> Allen, F. M. *Am J Surg*, to be published. *Transfusions and Polycythemia in Normal and Tumor-Bearing Rats*. *J Lab & Clin Med* **25**: 471-475, 1940. *Influences of Local Asphyxia, Organ Extracts and Temperature Changes on Ingrafted Subcutaneous and Visceral Tumors in Rats*, *Urol & Cutan Rev* **44**: 1218, 1940.

## 2 MOUSE TUMORS

Seven mice with large tumors were received. Small biopsy specimens were examined by Dr A S Price, of the Polyclinic Hospital, who furnished the microscopic diagnoses of 1 mammary adenoma, 1 adenoma with early malignant change and 5 carcinomas. Attempts to transplant the tumors into other mice failed. All these tumors showed typical hemorrhagic congestion, and all visible tissue sloughed completely after ligations of only one and one-half to three hours, while the legs or other normal structures included in the ligatures were unharmed. Some of the tumors were so situated that the entire mass could not be surrounded by a tourniquet. Others were so large that their necrosis resulted in the death of the mouse. One cure with survival was obtained. The animal had an inguinal carcinoma measuring 1.5 by 1.2 by 1 cm. The ligature was placed so as to include the tail and the rectal and vaginal openings but not the leg. After release in one and one-half hours there was the usual dark congestion of the tumor and pink hyperemia of the normal parts, followed by rapid sloughing and subsequent healing of the ulcer.

These results, together with the observations on chicken sarcoma, sufficed to prove that native tumors break down under asphyxia in the same manner as do implanted tumors. The ease of such breakdown is independent of the native or foreign origin of the tumor and likewise of the tissue type of malignancy. Thus, the benign rat fibroma succumbs more easily than the transplanted rat sarcoma or carcinoma. The native adenoma or carcinoma of the mouse is fully as sensitive to asphyxia as the transplanted mouse tumors and much more sensitive than the transplanted rat tumors. An analogy may be drawn with the variable radiosensitivity of different human tumors and with the fact that transplanted tumors in general are not more radiosensitive than native tumors.

## 3 DOG ADENOCARCINOMA

A dog which was to be killed because of tumor was donated to me by a veterinarian, Dr Frank Bloom of Flushing, L. I. It was a gray Cairn terrier, female, vigorous, slightly obese and not markedly senile. There were two subcutaneous masses, one on each side of the midline of the abdomen, near the costal margin, about the size of an egg and a walnut respectively, about 8 cm. apart and both hard and nodular. The tentative diagnosis of mammary adenocarcinoma was confirmed by a biopsy of material from the larger tumor.

With the dog under pentobarbital sodium anesthesia a clamp was passed deep beneath the center of the large tumor, through cutaneous punctures about 2 cm. from its margin, carrying two rubber ligatures. This procedure was repeated in a line at right angles to the first. By tying off the four quadrants thus created all blood supply was cut off from the large tumor. The ligation was maintained

for six hours. In a small animal, such as a rat, the direct pressure of ligatures for this length of time without protection of the skin ordinarily results in obliteration of vessels and sloughing of the entire mass, but the larger and tougher vessels of the dog resist the injury. Just before release it was discovered that a trifle of blood flow was present in the tumor, and the cause was found in the breaking of one of the strands of rubber. The tumor swelled greatly after release, but its color was not discernible. The inflammatory reaction and edema also extended over a considerable surrounding area and included the tumor on the opposite side. During the following week or two both tumors shrank gradually, until the large one was about half and the smaller one about two thirds of its original bulk.

One month after the first treatment, both tumors were stationary or showed very slight growth. A small biopsy specimen from the larger one resembled the former specimen except for considerable fibrosis. With the dog under pentobarbital sodium anesthesia a pair of rubber ligatures were passed under the center of the tumor through cutaneous punctures about 3 cm. from the margins, and the smaller size now permitted tying off in two halves. Complete stoppage of blood flow was thus maintained for four hours. The resulting inflammatory reaction was followed by a further slight shrinkage of both tumors. The large one in particular became noticeably flabby, in contrast to its original hard angularity. The normal tissues included with the tumor within the ligature in both treatments suffered no permanent damage.

Two weeks after the second treatment the tumors seemed to be stationary but not receding further. A third treatment was then given by ligating the large tumor in two halves for six hours. The result was immediate sloughing of all visible tissue in this tumor. The normal tissues included within the ligature were merely inflamed, with the exception of a small patch of skin over the center of the tumor, which was lost secondarily in the ulceration. The small tumor maintained its reduced size, without perceptible growth or recession.

One month after this third treatment the ulcer was healed down to a tiny superficial area, without sign of recurrence. The dog then escaped from the laboratory, so that the opportunity for treatment of the small tumor and final proof of cure was lost.

The experiment was of particular interest for two reasons: first, the partial recession obtained in the first treatment when the blood flow was not completely stopped, second, the partial recession in the smaller tumor, which was not ligated but was merely involved in the spread of inflammation from the treated tumor. The conditions here seem to resemble those in some cases of recession of human tumors in the literature. These conditions had not been reproduced in any of the tumors of rodents, in spite of the utmost efforts in this direction from the beginning of the research. In rats and mice ligation either causes immediate sloughing of a tumor or leaves it in active growth. In rats, at least, tests showed inflammation to be ineffectual without asphyxia. It was therefore of great interest to find a suggestion of radical differences in behavior of tumors due to species.

#### 4. HUMAN CANCER

Two cases were studied in an attempt to apply some of the experimental results and also to gain additional information.

## REPORT OF CASES

CASE 1—Mrs J D, aged 48 years, was referred to me by Dr Edward A Kellogg. In 1929 Dr Kellogg had removed the left breast for a tumor which was diagnosed microscopically as a scirrhus carcinoma of mammary duct origin. The patient appeared in perfect health until September 1935. Then, after this unusually long latent period of six years, a small cervical swelling appeared. On September 9 glands were removed, which were found microscopically to contain tumor identical with the original one. Another cervical swelling led to removal of another group of glands on October 1, and still others were excised on Jan 3, 1936, with the same microscopic picture in all. Roentgen treatments were given to the limit of safety without any effect. Increased rapidity of tumor growth was evident. The patient was seen in consultation on March 3 and received experimental treatments at short intervals from that date until her death from intrathoracic metastases on December 14.

On March 3 the left side of the neck showed five healed scars in different areas where glands had been removed. There was a sprinkling of hard superficial glands from shot to bean size over the left side of the neck, from the midline in front to the midline behind. A fused clump of such glands was palpable below the margin of the jaw. The only sign of deep glandular involvement was an almond-sized mass about midway between the jaw and the clavicle and adjacent to the carotid sheath.

It would have been preferred to try ligation of some of the easily accessible glands. The patient positively refused further surgical treatment of any description but was eager to cooperate in any other kind of experiment. Therefore, treatment was directed to attempts to imitate the local conditions of streptococcic infection. Most of the time was occupied with very mild applications of new measures, which were increased gradually enough to assure against harm. With many variations, the main procedures were as follows:

1 Potassium arsenite<sup>3</sup> was used as a nonirritating form of arsenic, and on one occasion arsphenamine was used as an irritating form. The method varied from injection of a few drops of undiluted solution of potassium arsenite U S P into the center of a small gland to infiltration of large volumes of high dilution over large areas. Because of a high individual tolerance or for other reasons, it was possible to raise the dose as high as 1 cc without signs of intoxication. Procaine hydrochloride or sometimes cocaine hydrochloride was included in the solution, together with epinephrine hydrochloride and sometimes also ephedrine hydrochloride. Stoppage or reduction of circulation was attempted in three general ways:

a Small injections were repeated every ten or fifteen minutes, so as to keep an individual gland and its immediate environment saturated with the arsenic for four to six hours continuously. The white wheal caused by the vasoconstrictor substances was always evanescent and was replaced by pink in spite of all efforts. Also, the hardness of the gland caused the fluid to escape from it into the loose tissues of the neck.

b The same solutions were used with the addition of dextrin or acacia to make as thick a mixture as would flow through the needle, so as to favor local pressure and diminish the spread through the tissues and also for the sake of possible prolonged tissue reactions to the colloids.

c On one occasion the solution was diluted to 1,500 cc., and the attempt was made to maintain local anemia by fluid pressure, fresh solution being injected whenever the tension diminished. Pressure sufficient to cause visible bulging of the pharynx on inspection inside the mouth was thus maintained for three hours and somewhat less pressure for two more hours, but the influence for preventing circulation was inadequate.

The breaking down of cancerous glands by methods *a* and *b* was more successful than might have been expected from the imperfect infiltration and anemia. This tumor, however, was highly resistant to arsenic, because it continued a slow, infiltrating growth after the glands were broken down. Method *c* accomplished nothing. It did not cause any breaking down of glands in the infiltrated area, and the subsequent appearance of new nodules proved that it failed in the main purpose for which it was used, namely, the killing of invisible deposits of cancer throughout the lymph spaces.

2 Pure glycerin, saturated solution of sodium chloride and other strong irritants were injected into cancerous glands, alone or with arsenic. These forms of inflammation proved to be unnecessarily painful without any helpful effects in killing cancer.

3 Injections of Coley fluid (a mixture of the toxins of erysipelas and *Bacillus prodigiosus* <sup>4</sup>) with cocaine or procaine hydrochloride, epinephrine and sometimes arsenic were made at intervals of fifteen to thirty minutes, so as to keep individual glands saturated with the streptococcus toxin (with or without arsenic) for several hours. Sometimes these treatments were repeated over a series of days. Glands were thus broken down, but more or less infiltrating growth continued. With ascending doses of Coley fluid the additional influence of fever was tested, with rectal temperatures up to 103.4 F., but without any striking change in the results.

4 One gland together with its immediate environment was infiltrated with a starch suspension on two days, causing a mild chronic inflammatory reaction. A biopsy specimen was obtained, and Dr. A. S. Price, without knowing what had been done, made a microscopic diagnosis of carcinoma together with "foreign body granulomatous reaction and multinucleated giant cell formation." The tumor growth was not arrested.

Several applications of roentgen rays were made by Dr. A. J. Quimby according to two plans.

a In view of the reported dangers of the combination of roentgen therapy and some arsenicals,<sup>5</sup> it was desired to learn whether the tumor might be more sensitized than the normal tissues and also what the effect would be when the tissues were directly infiltrated with arsenic in far higher concentration than could result from any systemic administration. From cautious beginnings with minimal doses of both the drug and the rays (over small areas) advances were made gradually to full erythema irradiation and 1 cc. of solution of potassium arsenite U. S. P. A systemic action must also have resulted from absorption of the injected material. Nevertheless, there was no perceptible sensitization of either the tumor or the normal tissues. At least with regard to this single case, it had to be concluded that the fears concerning arsenic in connection with roentgen therapy were unfounded, there was also absence of benefit.

<sup>4</sup> Coley, W. B. Late Results of the Treatment of Inoperable Sarcoma by the Mixed Toxins of Erysipelas and *Bacillus prodigiosus*, *Am. J. M. Sc.* **131** 375-430 1906.

<sup>5</sup> Hueper, W. C., and Itami, S. Effects of Neoparsphenamine on Spontaneous Breast Tumors of Mice, *Am. J. Cancer* **17** 106-115, 1933.



*b* While the first experiments were being performed on the superficial glands, the mass of deep glands grew rapidly to walnut size. On account of their close proximity to the carotid sheath, pressure disturbances could be anticipated, and a problem of treatment was created. A hint was taken from the roentgen treatment of carbuncle. With a long, thin needle this mass was given daily injections of ascending doses of Coley fluid and arsenic. The increasing inflammation quickly produced the equivalent of an aseptic carbuncle, with the typical swelling, redness and induration but with only tenderness instead of severe pain. A single application of roentgen therapy ( $\frac{2}{3}$  erythema dose) was then given, and the entire mass promptly liquefied and discharged through a small opening. During the following six months of observation, no further swelling appeared in this region or anywhere in the deep cervical glands. There were no circulatory or nervous disturbances at any time.

The net result of all the treatments was an absence of distinct tumor masses or any increase of bulk in the affected side of the neck. The tissues were considerably indurated by the repeated inflammations and obviously also by a thin, diffuse growth of tumor. Three small sinuses were left, which discharged a trifle of serous fluid. All pressure symptoms were prevented, and as far as the neck was concerned there was no need for sedatives except briefly, at the time of the most strenuous treatments. In contrast, the intrathoracic growth gradually produced marked edema and pain in the left arm, requiring large doses of morphine toward the end.

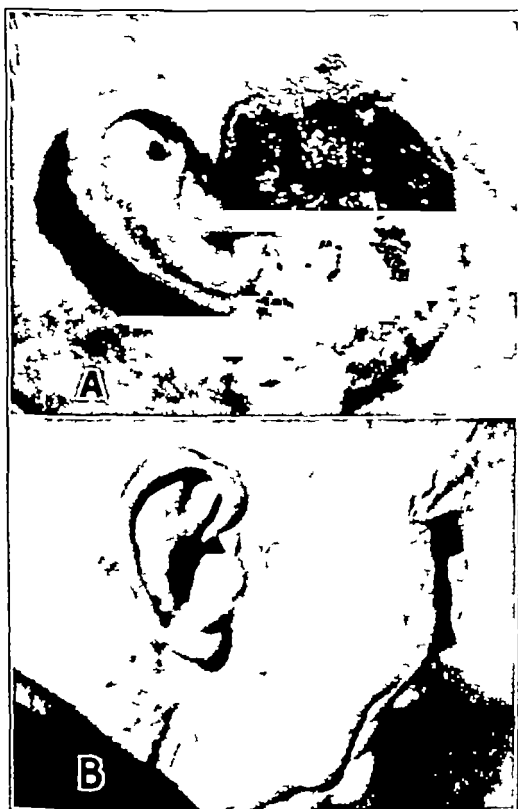
*Comment*—On the whole, this tumor was characterized by high resistance to arsenic and streptococcus toxin, in addition to the mechanical difficulties of infiltration. The question of its possible response to asphyxia remains unanswered. From this single experience and on general principles, it appears fairly probable that any tumor mass, even of a radioresistant type and in an inoperable location, can be broken down by converting it into an aseptic carbuncle by injections of any suitable inflammatory agents and then administering a moderate dose of roentgen radiation. The slough consists of the tumor and the inflammatory exudate, not the normal tissue, and blood vessels will presumably not be endangered unless there is actual invasion of their walls by tumor. The plan may possibly have some practical application in cases in which the direct pressure of tumor masses is serious. Whether any such local masses can be actually cured by the method is problematic and may depend on the type of the tumor and other special conditions. The conversion of a radioresistant into a radiosensitive tumor appears theoretically interesting.

CASE 2—W. H., aged 76 years, with senility, moderate obesity and myocardial degeneration, came to the dermatologic clinic of the Polyclinic Hospital with an ulcerated cancer of the face which was diagnosed microscopically as a squamous cell carcinoma. The treatment of a reputedly radioresistant tumor in this location presented difficulties. Permission to attempt it was granted by Drs. Frederick H. Dillingham and A. H. Montgomery, in charge of the clinic.

At the time of the patient's admission to the hospital, Oct. 2, 1935, the tumor was a fungating mass 5 by 8 cm., with the appearance and location shown in the accompanying illustration (A). On the following day, with the region under

local anesthesia, Dr Robert E Brennan placed a temporary ligature on the external carotid artery. Attempts were then made to produce anemia of the tumor by means of special splints, a rubber bandage and air compression. The effort had to be abandoned because of pain too great to be controlled by morphine and unsatisfactory arrest of circulation and also because direct pressure is different from simple anemia and endangers the normal tissues too seriously. The ligature was removed from the artery, and the cervical wound was closed.

On October 6 with the region under local procaine hydrochloride anesthesia, Dr Brennan made six punctures through the skin about the periphery of the



*A* lesion before treatment, *B* lesion after treatment

tumor and 1 to 1.5 cm from its margin. Rubber ligatures were passed through these openings and tied, but they left a little circulation in the tumor from the underlying parts. The ligatures were released after one and one-half hours. There was slight darkening of the tumor and hyperemia of the surrounding tissues. There were also slight facial palsy and slight sloughing of superficial layers of the tumor.

On October 10, Dr Brennan again inserted rubber ligatures and this time burrowed deeply with a clamp under the center of the tumor, after which the two halves of the tumor were ligated off with several rubber ligatures passed through the previous cutaneous punctures. With the posterior half the ear was also deprived of circulation. Complete asphyxia was thus maintained for three

and one-quarter hours. On release, the tumor immediately showed the deep blue color of typical hemorrhagic congestion, while the normal tissues flushed bright red, making a sharp line of demarcation. During the following days there was an equally sharp sloughing out of the tumor without loss of any normal tissue. The ulcer healed rapidly, and the partial facial paralysis passed off completely within two to three weeks. The result is shown in the illustration (B).

The microscopic slides and the patient were seen by staff members at the Memorial Hospital, where it was first pointed out that a nonulcerated induration indicative of an extension of the tumor was forming at the margin of the mandible, strictly outside the line of the former ligatures. The patient was pleased and grateful but positively refused any further surgical treatment for a lump which was giving him no inconvenience. When it reached the size of a large lima bean, he was persuaded to try an injection treatment. This was based on the current doctrine that certain tumors are killed in their deep parts by an arsenic paste applied on the surface, by a selective process which spares the normal tissues. In this event, the killing of the more remote parts of the tumor must be due either to the simple inflammatory reaction or to a specific action of arsenic dissolved in the tissue fluids. Starting from this premise, 0.5 cc of solution of potassium arsenite U. S. P. was added to 60 cc of physiologic solution of sodium chloride together with epinephrine hydrochloride and procaine hydrochloride. Small quantities were injected into the tumor approximately every ten minutes until the entire amount was used up (in two hours). The firm tissue here afforded favorable physical conditions, because the white wheal created by each injection lasted an appreciable time, and sufficiently frequent repetitions maintained a state of approximate bloodlessness through the entire period. The infiltration and saturation of the tumor were also satisfactory, without undue spreading of the solution. In contrast to the violent reaction to any caustic paste, the later effect was so trivial as to create the suspicion that nothing had been accomplished. Within a few days, however, the tumor was found to have disappeared. The patient lived, free from tumor, for two years and died of myocardial failure.

*Comment*—Two comments in particular are suggested. 1. A tumor in some other location would have been strongly preferable for a first trial of ligation, because there were inevitable misgivings that the ear might slough off. The animal experiments, however, seemed to give sufficient assurance that the normal tissues could endure much more than three hours of asphyxia. This cancer happened to be killed within the same period as a mouse tumor, but other types might require a considerably longer time. The specificity of the effect is strikingly displayed in the destruction of the tumor on the lobe of the ear without any residual defect in the normal tissues of the ear. 2. This tumor was obviously of a feeble type and a low grade of malignancy. Nevertheless it was of a type known to be more radioresistant than some highly malignant types. It is easily conceivable that this type of tumor, which is killed by a simple injection of arsenic, might happen to be cured by a streptococcic infection, but there are also records of much more formidable tumors which have disappeared or receded markedly under infection. Evidently, therefore, different types of tumor differ irregularly in their susceptibility to various injuries.

## GENERAL COMMENT

Cures of inoperable malignant tumors in man are attested by conclusive evidence and accepted by conservative authorities. The complete cures or extreme recessions number into the hundreds and fall into two classes: first, a few cases in which malignant growths have receded extensively or disappeared completely in connection with mild cellular reactions or under unknown conditions,<sup>6</sup> and second, a much larger group in which the recession or disappearance has resulted from severe infections, such as erysipelas (Fehleisen-Coley) or peritonitis accompanied by extreme fever and intoxication.<sup>7</sup> With the improvements in surgery, which have abolished most of these complications, the cures of inoperable malignant tumor have also ceased. Inasmuch as clinical clues have always furnished the best guidance for advances in knowledge and treatment, it is important to emphasize the cures or remarkable recessions that have occurred in cases of extensive glandular involvement and of pelvic cancer with visible metastases scattered over wide peritoneal areas. Apart from the spontaneous recessions the salient therapeutic point is found in the numerous assertions that the drastic use of heat in particular and to a less extent of caustics and other agencies<sup>8</sup> may be followed by death of deep tumor cells which have not

6 Rubens-Duval, H. Considerations sur les reactions de l'organisme a l'egard du cancer et la therapeutique anticancereuse. *Progres med.*, 1931 pp 609-619.  
Hodenpfl, E. Treatment of Carcinoma with the Body Fluids of a Recovered Case, *M Rec* **77** 359-360, 1910. Handley, W S. The Natural Cure of Cancer, *Brit. M J* **1** 582-589, 1909. Mackay, C G. A Case That Seems to Suggest a Clue to the Possible Solution of the Cancer Problem, *ibid* **2** 138-140, 1907.

7 Rohdenburg, G L. Fluctuations in the Growth Energy of Malignant Tumors in Man with Especial Reference to Spontaneous Recession. *J Cancer Research* **3** 193-225, 1918. DeCourcy, J L. Spontaneous Regression of Cancer, *J Med* **14** 141-146, 1933. Rosenrauch, C. A propos de l'erysipele salutaire et de son action therapeutique sur les tumeurs malignes, *Clinique Paris* **28** 324-326, 1933. Fehleisen, F. Die Aetologie des Erysipels, Berlin, T. Fischer, 1883, cited by Coley, W B. The Treatment of Malignant Tumors by Repeated Inoculations of Erysipelas with a Report of Ten Original Cases. *Am J M Sc* **105** 487-511, 1893. Lindenstein L. Bemerkungen zu der Arbeit von Prim Dr A. Müller. "Als Beitrag zum Kapitel Erysipel und Karzinom." *Zentralbl f Chir* **59** 2531-2532, 1932. Müller, A. Als Beitrag zum Kapitel "Erysipel und Karzinom," *ibid* **59** 1684-1685, 1932. Lomer, R. Zur Frage der Heilbarkeit des Carcinoms. *Ztschr f Geburtsh. u Gynäk* **50** 305-384, 1903. Mohr, H. Ueber spontane Heilungsvorgänge beim Karzinom, *Therap Monatsh* **17** 553-560, 1903.

8 Theilhaber, A. Zur Lehre von der Spontanheilung der Karzinome, *Deutsche med. Wchnschr* **38** 1240-1241, 1912. Watson, J. Butyric Acid in the Treatment of Cancer. *Lancet* **1** 746-748, 1933. Byrne, J. A Digest of Twenty Years Experience in the Treatment of Cancer of the Uterus by Galvano-Cautery. *Am J Obst* **22** 1052-1053, 1889. Vaginal Hysterectomy and High Amputation, or Partial Extirpation by Galvanocautery in Cancer of Cervix Uteri. An Inquiry into Their Relative Merits. *Brooklyn M J* **6** 729-760, 1892. *Tr Am Gynec Soc* **17** 3-41, 1892.

been directly touched by the cautery or other agent. All these bizarre reports can be unified and utilized more intelligently with the understanding that the production of a certain kind and degree of inflammatory reaction is the essential basis of all effective treatment of this kind.

The principal new viewpoint to suggest, therefore, is that the examples of infectious cure of neoplasms have been in the main misinterpreted and that the curative agency which was sought in the form of a systemic intoxication is really to be found in the local inflammatory reaction. It is impossible to overlook the similarity of action of ligation, arsenic and streptococcus or other bacterial toxins in causing edema, inflammation, capillary permeability changes and sometimes hemorrhages. A severe local infection often creates tumefaction and induration, which is illustrated on a large scale in a carbuncle. The pressure and lack of circulation in the interior may reach the point of necrosis, but in the zones outside this there must also be an abnormal state of circulation and cell nutrition. This state of partial asphyxia seems to favor destruction of the tumor in somewhat the same way as does ligation. On the other hand, strong sodium chloride solutions and similar irritants produce an inflammatory area which is bright red throughout. This type of inflammation never destroys experimental tumors and may even hasten their growth, and the same may be true of some types of infection.

There appear to be at least five illustrations of efficient protection against tumors by local tissue reactions.

- 1 The local "immunity" conferred by light roentgen therapy against implantation of experimental cancer.<sup>9</sup>

- 2 The cure of certain cancers by local applications of arsenic and other chemicals. The mode of action of these substances is still uncertain. Granting, however, that there is a destruction of deep cells not in direct contact with the medicament, it seems scarcely probable that such a diverse group of substances should all be specifically toxic for tumor cells in distinction from normal cells, but all these substances share the common property of setting up inflammatory or tissue reactions, which may plausibly account for the selective tumor destruction.

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<sup>9</sup> Da Fano, C. Zelluläre Analyse der Geschwulstimmunitätsreaktion, *Ztschr f Immunitätsforsch* 5 1-75, 1910. Murphy, J. B., and Sturm, E. J. The Lymphocyte in Natural and Induced Resistance to Transplanted Cancer. Effect of Dry Heat on Resistance to Transplanted Cancer in Mice, *J Exper Med* 29 25-34 1919. Murphy, J. B. The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease, and Tuberculous Infection, Monograph 21, Rockefeller Institute for Medical Research, 1926.

3 The cure of transplanted mouse tumors by injections of starch (Chambers and Grand <sup>10</sup>) through a lymphocytic reaction in line with earlier theories,<sup>9</sup> and the slightly different natural defensive reaction in resistant animals <sup>11</sup>

4 The spontaneous recession or cure of malignant tumors in human patients,<sup>12</sup> sometimes under slight or unknown influences but mostly due directly to severe infection or inflammation

5 The partial or complete breakdown of tumors following the asphyxia produced by ligation

These reactions appear to differ in character and degree. Nos 1 and 3 are mild in their effects and apparently feeble in potency, the tissue reaction to roentgen therapy <sup>13</sup> is not accepted by authorities as curative, the reaction to starch seems to cure only the highly sensitive mouse tumors, but some equally mild accidental reaction may have cured a few especially sensitive human tumors. The other curative reactions, to ligation, caustic applications and infections, are more violent and apparently more powerful. Arsenic may hold an intermediate place, since the ordinary arsenic pastes set up severe inflammation, but arsenic solutions cause minimal irritation, and in case 2 (this paper) it proved possible to cure a feeble tumor by arsenical infiltration together with partial anemia. It is only by rare accident or in the case of the feeble tumors that any of the aforementioned tissue reactions alone suffices to effect a cure. The best results seem to be promised by suitable combinations. To some extent every foreign or new growth seems susceptible to this form of attack. Thus, both tumor tissue and normal granulation tissue break down under ligation, and when a tumor is converted into an inflamed mass by repeated injections of toxin a roentgen treatment liquefies the tumor and the inflammatory exudate but not the normal tissues.

Obviously, this entire work is strictly in an experimental stage. Extensive research is necessary to discover the nature and the most favorable forms and combinations of the agents for provoking tissue reaction. Actual ligation is seldom applicable, and, though the possibility has been suggested for certain bone sarcomas, many contingencies

10 Chambers, R, and Grand, C G. The Effect of Injecting Starch Grains into Transplanted Tumors, *Am J Cancer* **29** 111-115 1937

11 Roussy, G, Leroux, R, and Pevre, E. Le cancer de goudron chez la souris, *Presse med* **30** 1061-1065, 1922

12 Footnotes 6 and 7

13 (a) Sittenfield M J. A Method to Render Radioresistant Tumors Radio Sensitive *Radiology* **22** 490-492, 1934 (b) Allen, F M. Local Asphyxia and Roentgen Irradiation of Transplantable Rat Tumors, *Am J Roentgenol* **42** 745-755 1939

of failure or danger must be gravely considered. It seems justifiable to make tests of isolated superficial nodules in cases of inoperable tumor in order to learn the response of different tumor types, with the foreknowledge that problems of technic remain to be solved and that some tumors may prove entirely resistant. The combination of toxic inflammation and roentgen therapy<sup>17b</sup> may approach closer to practical application, for example, in breaking down gross masses, as has been suggested. Furthermore, when a surgeon removes a radioresistant tumor and suspects metastases in a definite area, he commonly goes through the ceremony of ordering roentgen treatment, hoping that it will help while knowing that it will not. It is theoretically possible that the production of a suitable kind and degree of inflammation may sensitize the subject in such a manner that the roentgen rays can actually kill metastases in certain regions, for example, the chest wall, the neck or the pelvis.

#### SUMMARY AND CONCLUSIONS

Resistance to asphyxia varies with the type of tumor and perhaps with the animal species but not in any uniform way with the foreign or native origin of the tumor. Some spontaneous tumors are far more easily cured by asphyxia than are some transplanted tumors.

An account is given of 2 patients in whom tumors were treated by asphyxia or by chemical methods aimed to produce similar local reactions. The tumor in 1 of the cases was highly resistant. In the other case, the main mass of a squamous cell carcinoma of the skin was made to disappear by temporary asphyxia, and a similar result occurred in the remaining portion after infiltration of a nonirritant arsenic solution under such pressure as to maintain relative anemia for a period.

The principal general deductions are (a) that the great mass of nonoperative cures or recessions of malignant tumors reported in the literature can be brought into unified comprehension on the basis of a reaction in the normal tissues, usually associated with inflammation, and (b) that the cure of properly selected tumors may sometimes be favored by the adjuvant action of two or more agents tending to set up this reaction. Further investigation along this line is believed to be warranted not only by the present results but by this interpretation of the literature.

## SPLENECTOMY IN THE TREATMENT OF BANTI'S SYNDROME

E H BARG, M D

AND

I W DULIN, M D

IOWA CITY

Since 1922, 43 patients have fulfilled the requirements for a diagnosis of Banti's syndrome at the State University Hospitals. Half of these patients were treated by splenectomy, and the remainder were treated conservatively. A comparison of the two groups was made in an effort to determine the effects of splenectomy.

This syndrome was separated from other splenic enlargements by Banti<sup>1</sup> in 1883, 1894 and 1910 and is frequently spoken of as Banti's disease. In 1900, Osler<sup>2</sup> reported a series of cases of a similar condition, which he called splenic anemia. The two terms are used interchangeably both in the United States and on the Continent. The English and German authors reserve the term Banti's disease for the advanced condition, with marked cirrhosis of the liver. American writers also include under the terms splenic anemia and Banti's disease splenomegaly with anemia caused by syphilis, tuberculosis and malaria.

The cause of Banti's disease is unknown. Banti and many workers (Yates, Bunting and Kristjanson,<sup>3</sup> Gibson<sup>4</sup> and Peel<sup>5</sup>) have attempted the isolation of causative micro-organisms. Recent etiologic theories include circulatory obstruction, such as direct or indirect stasis of the splenic vein as described by Rousselot<sup>6</sup> in 1936.

In this series there were no specific pathognomonic changes in the spleen. The spleen retained its normal gross contour. In the cases in which we operated the average weight of the organ was 800 Gm. The

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From the Department of General Surgery, State University Hospitals.

1 Farley, D. L. Banti's Disease in Piersol, G. M., Bartz, E. L. and others. *Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1932, vol. 6, p. 680.

2 Osler, W. *Am J M Sc.* **119** 54, 1900.

3 Yates, J. L., Bunting, C. H., and Kristjanson, H. T. The Etiology of Splenic Anemia or Banti's Disease, *J A M A* **63** 2225 (Dec. 19) 1914.

4 Gibson, A. G. *Quart J Med* **7** 153, 1914.

5 Peel, A. A. F. *J Path & Bact* **31** 591, 1928.

6 Rousselot, L. M. Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome. Clinical and Pathologic Study of Thirty-One Cases with Late Results Following Splenectomy, *J A M A* **107** 1788 (Nov. 28) 1936.



surface was usually covered with vascular adhesions, and the capsule was markedly thickened. There was an increased amount of fibrous tissue in the splenic framework and pulp. Frequently the splenic vein showed evidences of phlebitis, thrombosis or phlebosclerosis. We have observed at the time of operation several instances in which the splenic vein was greatly enlarged. On microscopic examination of the spleen there was marked fibrosis, the malpighian bodies were small and widely separated, and siderotic nodules were frequent. In the liver varying degrees of lobular cirrhosis were observed.

Since Banti's original description the disease has been divided into three stages. In the first stage the patient has splenic enlargement with or without mild secondary anemia. It has been thought that this stage lasts from three to five years. The second stage follows, is transitory and consists of increase of the symptoms and signs observed in the first stage plus hepatic enlargement, occasional attacks of icterus and pain in the upper part of the abdomen. In the third, or terminal, stage the hepatic symptoms predominate, with the appearance of ascites and esophageal or gastric hemorrhages. Because of the difficulty in the division of these stages, a more satisfactory classification divides the disease into a nonascitic and an ascitic stage.

Although in this series the syndrome usually appeared in the third decade of life, the patients varied from 5 to 75 years of age, 6 being children under 16 years of age. The average age of the surgically treated group was 35 years, and that of the group on whom no operation was performed was 43 years. The two sexes were about equally affected. The duration of symptoms averaged five years in the group on whom splenectomy was performed and four years in the group that did not undergo splenectomy.

The onset of the symptoms was often insidious. Gastroesophageal hemorrhages were often the first manifestation of the disease. Such hemorrhages are due to a rupture of gastroesophageal varices and may be small and repeated or massive with occasional exsanguination. The diagnosis of hemorrhage may be based on hematemesis or on the finding of blood in the stools. In our series 39 per cent of the patients had hematemesis. This represents a smaller per cent of cases of bleeding from varices than was reported in Chaney's<sup>7</sup> or Pemberton's<sup>8</sup> series. Epistaxis occurred in 25 per cent of the cases. Owing to the perisplenitis, recurring attacks of pain in the left upper abdominal quadrant were frequent. Occasionally the patient complained of gradually increasing size of the abdomen, due to the enlarged spleen, to the enlarging liver,

7 Chaney, W. C. *Am. J. M. Sc.* **165** 856, 1923.

8 Pemberton, J. de J. *Ann. Surg.* **94** 755, 1931.

to ascites or to a combination of the three. Edema of the lower extremities occurred late in the course of the disease. Icterus rarely appeared. Low grade fever, with temperatures varying from 100 to 102 F, was present in 32 of the cases.

The degree of anemia increased with the duration of the disease and the frequency of hemorrhages. The average red blood corpuscle count was 2,930,000 per cubic millimeter, and the hemoglobin content of the blood was 50 per cent of the normal. In addition to the anemia there were associated leukopenia and relative lymphocytosis. The average leukocyte count was 3,700 per cubic millimeter, with relative lymphocytosis in 15 instances. Lymphocytosis (50 to 60 per cent lymphocytes) was common. In 47 per cent of cases the blood platelet count was below normal. The coagulation time, bleeding time, clot retractility and fragility of the red blood corpuscles were within normal limits. In 3 instances the Wassermann reaction of the blood was positive for syphilis. The condition in these cases was classified as syphilitic Banti's disease, and the patients received treatment for syphilis in addition to splenectomy.

The diagnosis is usually made by exclusion. Among the more common entities which may simulate the condition are the leukemias, Hodgkin's disease, familial and acquired hemolytic icterus, pernicious anemia, thrombopenic purpura, Gaucher's disease and Niemann-Pick disease. In cases of cirrhosis of the liver with secondary splenomegaly it may be impossible to differentiate the two conditions. It is thought that in the last-mentioned condition the cirrhosis is primary and the splenic enlargement is secondary. Occasionally, differentiation between early Banti's disease and unusual types of tumor masses in the left upper abdominal quadrant is difficult. Retroperitoneal sarcoma, hypernephroma, pancreatic tumor and enlargement of the left lobe of the liver have been confused preoperatively with splenomegaly. Our demonstration of the splenic notch by physical examination was inaccurate in many of these cases.

Splenectomy was performed on 22 patients, with 6 operative deaths. Postmortem examinations were performed on all 6. Three of the deaths occurred in patients over 60 years of age. In 3 of the 6 the disease was in the nonascitic stage. Three of the deaths were a result of hemorrhage occurring from the operative site. One patient, who died on the eighth postoperative day, was found to have massive thrombosis of the superior and inferior mesenteric veins. In 1 instance death occurred on the tenth postoperative day as a result of multiple pulmonary infarcts. In the sixth instance, death (of a patient 66 years of age) was due to cardiac failure. Two additional patients died in the hospital

In 1 instance death was due to hemorrhage from the deep epigastric vessels following a paracentesis. In the other the patient died two months postoperatively of a massive hemorrhage from a ruptured esophageal varix.

Of the 14 patients who left the hospital, 12 have been followed. At the time of writing, 3 have died from gastroesophageal hemorrhage and 1 from an unknown cause. Four are alive and have been free of all symptoms for nine years, seven years, five years and two years since splenectomy. Two are much improved after three years and one year respectively, their only complaints being weakness and malaise. One of the remaining 2 patients states that she is symptomatically well, however, she has had occasional esophageal hemorrhages during the ten years following splenectomy. The remaining patient has lived five years and in this interval has had several minor esophageal hemorrhages and requires frequent paracentesis. Two of the 5 patients who preoperatively had gastroesophageal hemorrhages have continued to have such hemorrhages. In 4 patients this symptom developed for the first time after splenectomy, resulting in death in 3 instances. One of these is of interest because the hemorrhage first appeared eight years after operation.

Splenectomy had a favorable influence on ascites. Of 6 patients who preoperatively had required repeated paracentesis, only 1 has continued to have reaccumulations of abdominal fluid. The others have had no recurrence for seven years, five years, three years, two years and one year respectively. In the nonascitic group no instance of ascites occurred postoperatively.

There were no permanent ill effects attributable to removal of the spleen. The blood platelets rapidly rose, occasionally to 25 per cent volumetrically, and gradually returned to a relatively normal level over a period of weeks. The red blood corpuscles were temporarily increased. The early leukocytic response varied, the counts ranging from 15,000 to 40,000 white blood cells per cubic millimeter, with a decline to normal within four weeks. In a few instances there was a slight increase in the fragility of the red blood corpuscles.

Of the 21 patients on whom splenectomy was not performed, 6 are known to be living. Two have had fair general health for nine years and four years respectively. The latter has an occasional small gastroesophageal hemorrhage. In the remaining 4 cases the condition was diagnosed within the last two and one-half years. Two of the patients have had a progressive increase in their symptoms. Eleven of this group are known to be dead. One lived for three years, and all the others died within one year after discharge from the hospital.

## COMMENT

From our review of these cases of Banti's disease, we believe that splenectomy is the treatment of choice and should be performed in the early stages. The procedure may be contraindicated for elderly patients because of the high operative mortality. However 3 of our patients who were over 60 years of age have been greatly improved after operation. In our experience splenectomy, for some unexplainable reason has relieved the patients of their ascites. Whether this is due to a lessening of the circulatory load through the liver has not been proved. Undoubtedly an extensive collateral circulation is developed between the region of the splenic bed and the abdominal parietes. We do not perform an omentopexy although in some of our recent cases the greater omentum has been rotated into the splenic bed, as it is felt that this increases the collateral circulation. Splenectomy has not assured relief of gastroesophageal hemorrhages. In general, patients with rapidly developing symptoms before operation respond poorly to splenectomy.

## SUMMARY

Forty-three cases of Banti's syndrome were reviewed.

Splenectomy was performed on 22 patients.

There was an operative mortality of 27 per cent.

Hemorrhage from the operative site accounted for 50 per cent of the mortalities.

Duration of life was prolonged after splenectomy.

Ascites was relieved after splenectomy.

Gastroesophageal hemorrhages frequently continued or appeared for the first time after splenectomy.

# DEMONSTRATION OF A CAPILLARY PERMEABILITY FACTOR IN TISSUE EXTRACTS FROM NORMAL RABBITS

R H RIGDON, M D

NASHVILLE, TENN

Recently it has been shown that trypan blue after intravenous injection localizes and concentrates in areas of inflammation produced by the local application of xylene in the rabbit's skin only when the dye is given immediately or within approximately three hours after application of the irritant. Three hours after application of the xylene the skin shows all the cardinal features of inflammation. A second application of xylene to this area of inflammation immediately before the intravenous injection of trypan blue apparently produces some change in the tissues and capillaries that permits the localization and concentration of the dye in the area.<sup>1</sup>

The studies of Rous and Smith<sup>2</sup> have shown that colloidal dyes escape from the capillaries in the skin and the adjacent part of the venules. A definite gradient of permeability occurs in the small blood vessels. After local application of an irritant the dye escapes from a larger portion of these same vessels than occurs under normal conditions. The rapid accumulation of trypan blue in areas of skin recently treated with xylene suggests either that xylene acts directly on these capillaries and venules or that an intermediate substance is liberated by the tissue which acts on the endothelium of the capillaries to make them more permeable to this colloidal dye.

The failure of trypan blue to localize and concentrate in the skin after an intradermal injection of xylene may indicate that the substance responsible for the increase in capillary permeability is present only in the squamous epithelium. At least, it appears that it is present in a greater quantity in the epithelium than in the dermis.

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From the Department of Pathology, Vanderbilt University Medical School  
Aided by a grant from the Division of Medical Sciences, Rockefeller Foundation

1 Rigdon, R H. Capillary Permeability in the Skin of the Rabbit, *Proc Soc. Exper Biol & Med* **42** 43-45, 1939

2 Rous, P, and Smith, F. The Gradient of Vascular Permeability. Gradient Along Capillaries and Venules of Frog Skin, *J Exper Med* **53** 219-242, 1931

This theoretic substance differs from leukotaxine in that it is present in saline extracts from normal tissue, while leukotaxine occurs only in areas of inflammation, according to Menkin<sup>3</sup>

The present study is a report of the demonstration of a substance obtained from a saline extract of normal rabbit tissues which will produce an increase in capillary permeability after intradermal injection in the rabbit, as shown by the localization and concentration of trypan blue

#### MATERIAL AND METHODS

The tissues which have been most frequently studied are skin, muscle and testicle. These are cut into small pieces and then pounded in a mortar with a pestle. Saline solution is added during this process of maceration. The extracts are then centrifuged, and the supernatant fluid is used for intradermal injection into the skin of normal rabbits.

In the earlier preparation of the extract no definite quantity of either tissue or saline solution was used, however, in the later experiments the following arbitrary amounts were employed

	Group A		Group B	
Tissues	Weight, Gm	Saline Solution, Cc	Weight, Gm	Saline Solution, Cc.
Testicle	10	15	23	15
Skin	12.6	20	19.0	20
Muscle.	12.6	25	10.0	20

To compare the crude leukotaxine which Menkin<sup>3</sup> obtained from inflammatory exudates with the extracts of normal tissue, 0.7 cc. of a 10 per cent concentration of croton oil in olive oil was injected into the left pleural cavity of the same rabbit from which the tissues were removed from group B. The oil was injected forty-three hours before the animal was killed. Approximately 45 cc of cloudy straw-colored fluid was aspirated from the pleural cavity. This fluid was centrifuged, and the supernatant liquid was tested for the permeability factor. The control preparation for the pleural exudate was made by thoroughly mixing 0.7 cc of the same croton oil-olive oil mixture with 45 cc of saline solution.

The rabbits were carefully shaved twenty-four hours before the difference preparations<sup>3</sup> were injected intradermally. Two-tenths cubic centimeter of the extract liquid was injected at different intervals before 10 to 15 cc. of either a 0.2 per cent or a 0.4 per cent solution of trypan blue was injected into the veins of the ear. The skin was carefully observed before and after injection of the dye. Some of the animals were killed, and histologic sections were made from the skin to study the relation of the local accumulation of leukocytes to the localization and concentration of trypan blue.

#### EXPERIMENTS

Two rabbits were given injections of 0.2 cc of the three tissue extracts in group A at the following intervals before 10 cc of a 0.2 per cent suspension of trypan blue was given intravenously: area 1 three hours; area 2 two hours; and area 3 one hour. In area 4 the injection was given immediately before injection of the dye. Twenty-five minutes later trypan blue was present in areas 2, 3 and 4.

<sup>3</sup> Menkin V. Studies on Inflammation. *J. Exper. Med.* 64:485-502, 1936.

where the skin extract had been injected and only in areas 3 and 4 where the testicle extract had been given. No dye was present in any of the four areas where the muscle extract had been injected.

The three tissue extracts in group A were diluted in saline solution as follows: 1:10, 1:100 and 1:1,000. Two-tenths cubic centimeter of each was then injected into the skin of the same 2 rabbits approximately thirty minutes before the dye was given. Twenty-five minutes later a small amount of trypan blue was present in the areas where the 1:10 dilution of both the cutaneous and the testicular extracts had been injected in 1 of the 2 rabbits. No dye was present in either of these areas in the second rabbit. No dye was present in any of the areas where the muscle extract had been injected in either of the 2 animals.

One cubic centimeter of each of the three extracts in group A was placed in each of four test tubes (1 by 10 cm). These were then placed in a large boiler of water, and the temperature was gradually brought to 60 C. Ten minutes later one tube of each series was removed, after thirty minutes a second was removed, after forty minutes a third was removed and after sixty minutes the fourth was removed. The extract of muscle was coagulated when the first tube was removed from the water bath. The extracts of skin and of testicle became cloudy at this time, but they never coagulated. Two-tenths cubic centimeter of these heated tissue extracts was then injected intradermally into the same 2 rabbits approximately thirty minutes before the trypan blue was injected. Twenty-five minutes later the dye was present in all of the areas into which the heated cutaneous and testicular extracts had been injected in rabbit 1, while no dye was present in either of the areas in the second rabbit. It is obvious from these experiments that rabbits vary in their susceptibility to the substance responsible for the increase in capillary permeability.

The tissue extracts in group A were injected intravenously into 2 rabbits to study their effect on the blood pressure. The rabbits were anesthetized with pentobarbital sodium, and a cannula was put into the carotid artery. One and five-tenths to 4 cc of the different extracts was injected into the marginal veins of the ear. The blood pressure was not affected by any of the extracts.

There was a variation in the rate of diffusion in the tissues of the different extracts. When testicular extract was injected intradermally the bleb rapidly disappeared. The area of blue which developed after injection of trypan blue progressively increased in size in the areas where testicular extract was injected. Trypan blue localized first and the greatest quantity in the areas of skin treated with the skin extract, however, the dye did not spread as it did in the area treated with testicle. This variation in the localization of trypan blue in areas of skin treated with injected testicle extract as compared with skin extract is interesting in view of the characteristics attributed to testicular extracts by Hoffman and Duran-Reynals.<sup>4</sup>

The results obtained from the injection of the extracts in group B into 2 rabbits were the same as those observed with the extracts in group A. Trypan blue localized in the areas of skin treated with the skin and testicle extracts but did not localize where either the muscle extract or the pleural exudate had been injected. The dye did localize, however, in the areas where the saline suspension of croton oil and olive oil had been injected. These 2 rabbits were killed sixty minutes after injection of the trypan blue, and sections of skin were removed.

<sup>4</sup> Hoffman, D. C., and Duran-Reynals, F. The Influence of Testicular Extract on the Intradermal Spread of Injected Fluids and Particles, *J. Exper. Med.* 53: 387-398, 1931.

from the four areas treated with the extract of skin and from the four areas treated with the extract of muscle. There was a greater number of leukocytes in the tissue where the skin extract had been injected than there was in the areas of tissue treated with the muscle extract even in the same rabbit. There were essentially no leukocytes in the tissue where the extract of skin had been injected immediately before the dye was given. A tremendous number of polymorphonuclear leukocytes were present, however, in the area where the skin extract had been injected two and a half hours before the dye was given. As has been stated, trypan blue did not concentrate in the areas treated with the cutaneous extract two and a half hours prior to injection of the dye.

Skin from a normal rabbit was macerated in saline solution and centrifuged, and the supernatant fluid was filtered through a Berkefeld V candle. This sterile filtrate contained a substance that produced an increase in capillary permeability. Saline extracts of the liver and kidney also showed in the supernatant fluid a little of the substance which produces an increase in capillary permeability. The quantity, however, was much less than that present in extracts of the skin and testicle.

#### COMMENT

The demonstration of a substance in the saline extract of normal rabbit tissue that produces an increase in the permeability of the capillaries in the skin of the rabbit is interesting in view of Menkin's work on leukotaxine. My results confirm those of Bier and Planet.<sup>5</sup>

Leukotaxine, according to Menkin<sup>3</sup> is obtained from tissue that is the site of an inflammatory reaction. When injected intradermally it causes an increase in permeability as shown by the localization and concentration of trypan blue and also it produces a rapid emigration of leukocytes into the part. Leukocytes also appear in the tissue where the extract of normal skin is injected; however, when the greater number of leukocytes are present, trypan blue fails to concentrate in the area. The fact that trypan blue fails to localize and concentrate in all areas of inflammation produced by xylene suggests that the mechanism by which the capillaries become more permeable may not be the same as that responsible for the localization of leukocytes in areas of inflammation. The two processes may, however, occur together.

The failure of trypan blue to concentrate in areas of skin treated with injected extracts of skin and muscle when the dye is injected three hours after intradermal injection of the extracts is interesting in view of previous experiments in which xylene was applied to the skin.<sup>6</sup> These have shown that trypan blue does not concentrate in xylene-treated areas of skin when it is given intravenously approximately three hours after application of the irritant.

<sup>5</sup> Bier, O. and Planet, N. Sur la presence d'un facteur qui augmente la permeabilite capillaire dans les extraits de peau normale. *Compt rend Soc de biol* **129** 65 67 1938.

<sup>6</sup> Rigdon, R. H. Capillary Permeability in Areas of Inflammation Produced by Xylene. *Arch Surg* this issue p 101.



The wide variation in amount of the permeability factor in the different tissues suggests that the failure of trypan blue to localize in an area where xylene is injected intradermally may be due either to the small quantity of this substance liberated from the tissue in the subdermis or that the capillaries are too few in this area to permit escape of a sufficient quantity of the dye to color the tissue

It is possible that the same permeability factor may be present in both the cutaneous and the testicular extract. The variation in staining of the area with trypan blue may result from a difference in diffusion of the two extracts. The testicular extract may contain one or more substances that influence the rate of diffusion and only one that produces an increase in permeability of the capillaries

The capillary permeability factor present in the extracts of skin and testicle resembles the spreading factor of Duran-Reynal in that both are thermostable and filtrable. These tissue extracts when injected intravenously in normal rabbits have no effect on the blood pressure. Leukotaxine, according to Menkin, may produce either no change or only a transient and practically negligible fall in the cat's blood pressure.<sup>7</sup>

Trypan blue, when given intravenously after the intradermal injection of 2 mg of histamine diluted with distilled water, localizes about the margin of the bleb. The same dye localizes in the center of the areas treated with the injected extracts of skin and testicle. Subsequent studies will be necessary before any comparison of the substance obtained from saline extracts of normal skin and normal testicle can be made with histamine and leukotaxine. These crude extracts of normal rabbit tissue will be purified according to the method used by Menkin<sup>8</sup> to obtain crystalline leukotaxine

#### SUMMARY

A substance has been obtained from the skin, muscle and testicle of normal rabbits which produces a local increase in capillary permeability, as manifested by the localization and concentration of trypan blue. This substance is obtained by macerating normal tissue in saline solution

<sup>7</sup> Menkin, V., and Kadish, M. A. Studies on the Physiological Effects of Leukotaxine, *Am J Physiol* **124** 524-529, 1939

<sup>8</sup> Menkin, V. Studies on Inflammation, *J Exper Med* **67** 129-144, 1938

# CAPILLARY PERMEABILITY IN AREAS OF INFLAMMATION PRODUCED BY XYLENE

R H RIGDON, M D

NASHVILLE, TENN

The smaller blood vessels in areas of inflammation show an increase in permeability as manifested by an increase in the flow of fluid from the capillaries into the tissue spaces. This increase in permeability may also be shown by the localization and concentration of colloidal dyes. Many investigators<sup>1</sup> have observed the localization and concentration of blood-borne material in areas of inflammation. Burrows<sup>2</sup> has recently stated that "whenever inflammation occurs and from whatever cause, an increased permeability of the capillaries may be expected." Menkin<sup>3</sup> has also frequently emphasized the fact that trypan blue and other dyes after intravenous injection promptly accumulate in areas of inflammation.

Recently I reported that trypan blue and india ink do not always concentrate in areas of inflammation produced by local application of xylene to the skin of rabbits<sup>4</sup>. These substances concentrate in such areas only when they are injected into the circulation immediately or within less than five hours after application of the xylene. The skin treated with this irritant after five hours shows all the macroscopic and microscopic changes associated with inflammation.

In the present study observations have been made on the localization (after intravascular injection) of trypan blue, india ink, antitoxin and vaccine virus in the areas of inflammation produced by local application of xylene to the skin of the rabbit.

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From the Department of Pathology, Vanderbilt University Medical School.

Aided by a grant from the Division of Medical Sciences, Rockefeller Foundation.

1 (a) Kettle, E. H. The Demonstration by the Fixation Abscess of the Influence of Silica in Determining B. Tuberculosis Infections. *Brit J Exper Path* **5** 158-164 1924. (b) Hanger, F. M., Jr. Effect of Intravenous Bacterial Filtrates on Skin Tests and Local Infections, *Proc Soc. Exper Biol & Med* **25** 775-777 1928. (c) Menkin, V. The Accumulation of Iron in Tuberculous Areas. *ibid* **27** 1020-1022, 1930. Studies on Inflammation. *J Exper Med* **50** 171-180, 1929.

2 Burrows, H. Some Factors in the Localisation of Disease in the Body. Baltimore, William Wood & Company 1932.

3 Menkin, V. Role of Inflammation in Immunity. *Physiol Rev* **18** 366-418 1938.

4 Rigdon, R. H. Capillary Permeability in the Skin of the Rabbit. *Proc Soc Exper Biol & Med* **42** 43-45 1939.

# LOCALIZATION AND CONCENTRATION OF TRYPAN BLUE IN XYLENE-TREATED AREAS OF SKIN

Xylene was applied on a cotton swab to areas of normal skin. The degree of injury produced by this irritant is relatively uniform in the different areas of the same rabbit and also in different rabbits. Xylene was applied to the skin of a single rabbit at intervals varying from immediately to forty-eight hours before the dye was injected. The skin usually became hyperemic within two or three minutes after application of this irritant, and frequently it was edematous within ten minutes. The edema and hyperemia remained for several days, after which time the epithelium desquamated. Polymorphonuclear leukocytes apparently began to infiltrate the dermis within ten to fifteen minutes after the xylene was applied. Usually one and a half or two hours elapsed however, before any significant number of leukocytes reached this tissue. Polymorphonuclear leukocytes and mononuclear cells continued to infiltrate the xylene-treated areas for ten to twelve hours. At this time many of the superficial epithelial cells were pyknotic and necrotic. Small groups of these epithelial cells separated from the basement membrane, and the spaces were filled with fluid and leukocytes. After thirty hours many of the epithelial cells were necrotic. The leukocytic exudate apparently did not increase after this time.

The trypan blue was suspended in saline solution. Usually 10 cc of a 0.2 per cent solution was given intravenously. The marginal veins of the ears were used for these injections. Only macroscopic observations were made in determining the presence of trypan blue in the xylene-treated and in the untreated areas of skin. The xylene-treated skin became dark blue within five minutes when the dye was injected immediately after application of the xylene. When the irritant was applied twenty-four hours before the dye was injected the xylene-treated areas of skin stained the same color as the untreated skin. When xylene was applied to different areas of the skin of a single rabbit at ten minute intervals, trypan blue localized first and in greatest quantity in the area where the irritant was last applied before the dye was given intravenously. The relation of the time of localization of trypan blue after an intravenous injection to the application of xylene is shown in figure 1. Xylene was applied to the skin in area 1 ninety minutes before the dye was injected intravenously, in area 2, sixty minutes, in area 3, thirty minutes, in area 4, fifteen minutes, in area 5, five minutes, and in area 6, immediately before the dye was given. This photograph was made eight minutes after injection of the dye. At this time the greatest amount of trypan blue was present in area 6. There was a progressive diminution in the amount of dyes in areas 5, 4, 3 and 2. No dye was present at this time in area 1.

In this experiment the interval between the first application of xylene and the injection of trypan blue was too short to provide any accurate information with regard to the relation between edema and hyperemia and the localization of trypan blue. Xylene was similarly applied to the skin of another group of rabbits at intervals longer than those in the preceding experiment. The irritant was applied to the skin of 1 of these animals at the following time before the dye was injected intravenously: area 1, twenty hours, area 2, two and one-quarter hours, area 3, forty-six minutes, and area 4, four minutes. Edema and hyperemia were present in areas 1, 2 and 3 when the trypan blue was injected. One hour after the dye was given there appeared to be the same amount of dye in areas 1 and 2 as there was in the untreated skin. Areas 3 and 4 were dark blue at this time.

Xylene was injected intradermally in a group of rabbits. Edema and hyperemia were present twenty-four hours after an intradermal injection of 0.2 cc of this irritant. These areas after twenty-four to forty-eight hours showed necrosis of the subdermal tissue. Trypan blue when injected intravenously failed to localize in the areas where xylene was injected intradermally, although the dye was given immediately after injection of the xylene. This dye also failed to localize and concentrate in the areas of inflammation when the xylene was injected twenty-four hours previously.

Trypan blue will localize in areas of skin where xylene is applied twenty-four hours previously provided a second application of the irritant is made immediately before the dye is given. This dye also localizes and concentrates in the skin in areas where xylene is injected intradermally twenty-four hours previously if the irritant is also applied to the skin over the edematous and hyperemic areas immediately before the dye is given intravenously.

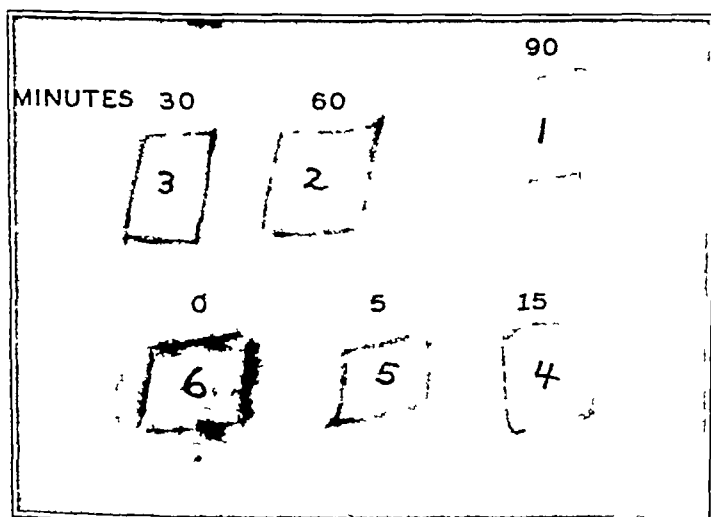


Fig 1—The number above each square gives the time in minutes that xylene was applied before 10 cc of 0.2 per cent trypan blue suspended in saline solution was injected intravenously. The number of the square is shown in the center of each. This photograph was made eight minutes after the dye was injected. The largest amount of trypan blue localizes in the area where xylene was last applied.

#### LOCALIZATION AND CONCENTRATION OF INDIA INK IN XYLENE-TREATED AREAS OF SKIN

India ink was used in this part of the experiment to determine whether it will localize and concentrate in areas of inflammation produced with xylene in a manner similar to that previously observed with trypan blue. Higgins' india ink was diluted in saline solution and the carbon suspension was injected into the left ventricle of the rabbit's heart. The quantity and concentration of the carbon suspension varied with the different animals. Some of the rabbits died immediately after injection of the ink while others survived from five to sixty minutes. Some of the rabbits were observed for five days after which time they were discarded.

Sections of the xylene-treated and of the untreated skin were removed and fixed in solution of formaldehyde. Paraffin sections were prepared and stained both with hematoxylin and eosin and with trinitrophenol. Portions of the different sections of skin were cleared in benzene and methyl salicylate to demonstrate the carbon particles in the capillaries.

Carbon particles suspended in saline solution localize and concentrate in areas of inflammation produced with xylene only when the suspension is given immediately or only a short time after application of the irritant. Macroscopic and microscopic studies show that the carbon particles circulate through the blood vessels in the normal skin and in all the areas of inflammation produced by xylene. The carbon concentrates only in areas where the irritant is applied a short time before the ink is injected. The carbon particles appear either to stick or to be phagocytosed by the endothelial cells in the small blood vessels. Only a few of the minute carbon particles ever reach the extravascular spaces. Polymorphonuclear leukocytes phagocytose some of the small carbon particles and apparently carry them into the extravascular tissues.

#### LOCALIZATION AND CONCENTRATION OF ANTITOXIN IN XYLENE-TREATED AREAS OF SKIN

Staphylococcus and diphtheria antitoxins were injected intravenously in different groups of rabbits in which the skin had been previously treated with xylene. The presence of antitoxin in the skin is determined by either absence of necrosis or a diminution in the size of the necrotic area at the point of injection of the toxin. The toxin was injected into both xylene-treated and the untreated areas of skin of the same rabbit. One-tenth cubic centimeter of four different dilutions of the diphtheria toxin was injected intradermally. The degree of necrosis was compared in the treated with that in the untreated area of skin.

Five cubic centimeters (approximately 1,750 units) of staphylococcus antitoxin was given intravenously, and xylene was immediately applied to an area of skin approximately 4 by 6 cm. One-tenth cubic centimeter of staphylococcus toxin was then injected intradermally into the xylene-treated and the untreated skin at intervals up to nine days. The same degree of necrosis occurred in the xylene-treated and in the untreated areas of skin when the toxin was injected intradermally, immediately after intravenous injection of antitoxin. When the toxin was injected intradermally from three and one-quarter to forty-four hours after intravenous injection of antitoxin there was a marked diminution and sometimes complete inhibition of the necrosis in the xylene-treated areas of skin as compared with the necrosis in the untreated skin of the same rabbit. Control experiments have shown that this inhibition of necrosis does not occur in rabbits with a similar inflammatory process and no antitoxin. When the staphylococcus toxin is injected into the xylene-treated area eight days after intravenous injection of the antitoxin, a similar degree of necrosis occurs in both the xylene-treated and the untreated areas of skin (fig. 2).

In this experiment with staphylococcus antitoxin no attempt was made to determine the length of time that could elapse between application of the xylene and intravenous injection of the antitoxin before the latter would cease to localize and concentrate in the areas of inflammation. This observation was made, however, with diphtheria antitoxin by the injection of 0.4 to 0.6 cc., approximately 1,000 units, at different intervals after application of xylene to the skin.

A group of 3 rabbits was given diphtheria antitoxin intravenously, and xylene was applied immediately thereafter to the skin. These animals showed a marked



Fig 2—A, xylene was applied in the area outlined with india ink. Five hours later 0.1 cc. of staphylococcus toxin was injected intradermally. Extensive necrosis was present after twenty-four hours. B, an equal amount of toxin was injected intradermally in an area of the skin of the rabbit shown in A. Approximately the same degree of necrosis occurred in the untreated as in the treated skin. C, xylene was applied to the area of skin that is demarcated from the normal by the zone of hyperemia forty-four hours before 0.1 cc of staphylococcus toxin was injected intradermally at the point indicated by the arrow. Essentially no necrosis occurred where the toxin was injected. D, a similar amount of toxin was injected into an area of untreated skin of rabbit shown in C. A large area of necrosis was present after twenty-four hours. E, xylene was applied in the area outlined with india ink nine days before 0.1 cc of staphylococcus toxin was injected intradermally. There was no edema or hyperemia present when the toxin was injected. Extensive necrosis occurred within twenty-four hours. F, a similar quantity of toxin was injected into an area of untreated skin of rabbit shown in E. An area of necrosis approximately the same size as that in the skin treated with xylene is present after twenty-four hours.

decrease in the size of the areas of necrosis produced by diphtheria toxin in the xylene-treated skin as compared with the necrosis in the untreated skin. The diphtheria toxin was given intradermally immediately after injection of the antitoxin. A second group, of 4 rabbits, was given the same quantity of diphtheria antitoxin, and immediately thereafter xylene was applied to the skin. Different dilutions of diphtheria toxin were injected intradermally four to six hours later. The necrosis in these animals was much less in the xylene-treated areas than in the normal skin. A third group of rabbits was given diphtheria antitoxin eighteen to twenty-four hours after application of xylene. Diphtheria toxin was injected intradermally four to six hours later. The areas of necrosis in these rabbits were approximately the same in the xylene-treated as in the untreated skin.

#### LOCALIZATION OF VACCINE VIRUS IN XYLENE-TREATED AREAS OF SKIN

A suspension of virus was prepared by macerating in saline solution the growth obtained from the membrane of a chick embryo. The larger particles were

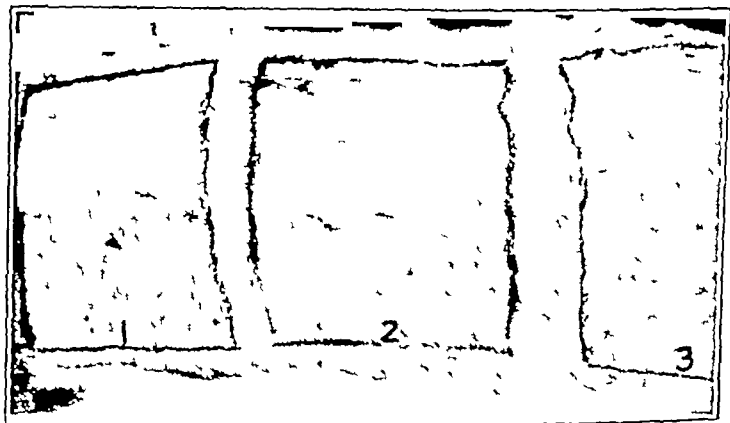


Fig. 3—Xylene was applied in area 1 twenty-four hours before the virus was injected. Area 2 is the untreated (control) area of skin. Xylene was applied to area 3 immediately after intravenous injection of 5 cc of a saline suspension of vaccine virus. The photograph was made on the seventh day after injection of the virus. At this time there were nine lesions in area 1, five in area 2 and thirty in area 3.

separated by centrifugation. One to 5 cc of this virus suspension was injected into the marginal veins of the ear. Xylene was applied to one area of skin twenty-four hours before the virus was injected and to another area of skin in the same animal immediately after injection of the virus. An area of skin of equal size was outlined for the control.

The number of vaccinal lesions that appeared in both the xylene-treated and the untreated areas of skin varied with the different rabbits. The greatest number of vaccinal lesions, however, always occurred in the area of skin where xylene was applied immediately after intravenous injection of the virus.

Approximately an equal number of lesions occurred in the normal skin and in those areas of skin treated with xylene twenty-four hours prior to intravenous injection of the virus. Figure 3 shows the vaccinal lesions in the two xylene-treated areas and in the normal skin. Xylene was applied over area 1 twenty-four hours before the animal was given the suspension of virus intravenously. Area 2

is normal skin Xylene was applied over area 3 immediately after injection of the virus Seven days after injection of the virus there were nine lesions in area 1, five in area 2 and thirty in area 3

Two rabbits in this group showed almost a confluent vaccinal lesion in the untreated skin over the back and only a few isolated lesions on the lower portion of the abdomen The hair subsequently grew much more quickly over the backs of these rabbits than along the lower part of the abdomen Two other rabbits showed focal collections of vaccinal lesions in areas where the hair was growing rapidly in both the xylene-treated and the untreated areas of skin

#### COMMENT

This series of observations shows that trypan blue, carbon particles, antitoxin and vaccine virus when injected into the circulating blood concentrate in areas of inflammation produced by xylene only during a specific interval The time in which these substances localize and concentrate in the xylene-treated areas of skin is not determined by the presence or absence of edema hyperemia and leukocytic infiltration of the skin In fact there is little edema or hyperemia at the time trypan blue localizes in those areas of skin where xylene is placed immediately before the dye is injected Furthermore, there may be all the macroscopic and microscopic changes commonly associated with inflammation, and still the dye may not concentrate

It is interesting that substances varying as widely as those used in this study all localize relatively the same with regard to the time of application of xylene and the intravenous injection of the substances This observation suggests that the capillaries become more permeable immediately after application of xylene and then gradually return to their normal state of permeability Apparently the capillaries require approximately three hours after application of xylene to return to their normal state of permeability At this time the skin may be edematous and hyperemic and leukocytes may be infiltrating the area

Foreign substances (those used in this experiment and many others) have frequently been found to localize and concentrate in areas of inflammation Hanger<sup>1b</sup> observed that after an intravenous injection carbon particles did not always localize in areas of inflammation There is a definite period in which these particles localize in the skin after intradermal injection of a filtrate of *Bacillus leprosepticus* The localization is explained on the basis of phagocytosis of the carbon particles by the capillary endothelium Fox<sup>1a</sup> likewise observed a definite period in which trypan blue hemolysins and agglutinins after intravenous

<sup>5</sup> (a) Fox J P The Localization and Concentration of Blood Borne Antibodies and Colloidal Dye in Areas of Inflammation of Various Ages *J Immunol* 31 283-308 1936 (b) Berlin M Antitoxine tetanique et absces de fixation *Compt rend Soc de biol* 102 731-733 1929 (c) Footnote 1



injection would concentrate in areas of inflammation. The failure of these substances to concentrate in an area of inflammation was explained by Fox on the basis of thrombotic occlusions. In the discussion of his work he stated "The demonstration of the relationship between the stage of inflammation and the ability of an inflammatory process to localize blood-borne materials is important for its bearing on clinical problems, and also in clarifying the concepts of Menkin<sup>6</sup> and Burrows.<sup>2</sup> Such a qualification of this newly emphasized attribute of inflammation may seem rather obvious, yet, as we have seen, neither of the above authors has given the matter adequate experimental consideration."

Irritants other than xylene have been used in this study of the localization of trypan blue in areas of inflammation. Trypan blue will localize and concentrate in areas of skin where staphylococcus toxin is injected intradermally provided the dye is given intravenously within thirteen hours after injection of the toxin. This colloidal dye when given intravenously will also localize in an area of the rabbit's skin where horse serum has been injected twenty-four hours previously. The greatest amount of dye localizes in the area of skin where the horse serum is injected immediately before the dye. Trypan blue in these experiments has not been observed to localize and to concentrate in areas of inflammation produced by the intradermal injection of infusion broth cultures of staphylococci when given intradermally eight and twenty-four hours previously. This dye when given intravenously also does not concentrate in areas of the skin where 10 cc of a 1 per cent solution of sodium chloride is injected intradermally. It does localize and concentrate, however, in those areas of the skin treated with a similar quantity of a 4 per cent sodium chloride solution, even in the same rabbit. Trypan blue fails to concentrate in the areas of skin when it is given intravenously sixty minutes after intradermal injection of this hypertonic salt solution.

Trypan blue is always retained for a much longer time in tissues which show inflammatory changes than in the normal skin. This study illustrated the importance of clearly differentiating localization and concentration from fixation or retention of trypan blue in inflammatory tissue. The former may occur in areas where there is no cellular evidence of inflammation, the latter occurs only in the areas that show such a reaction. The difference between localization and concentration of a dye and retention can be determined macroscopically by observing the tissue immediately after intravenous injection of the dye.

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6 Menkin, V. An Aspect of Inflammation in Relation to Immunity. *Arch Path* 12 802-828 (Nov.) 1931. A Note on the Mechanism of Fixation in an Area of Sterile Inflammation, *Proc Soc Exper Biol & Med* 30 1069-1076 1933.

A knowledge of the relation between increased capillary permeability and the diapedesis of leukocytes is important in any consideration of inflammation and immunity. A consideration of the mechanism of capillary permeability based on experimental studies will be subsequently reported.

#### SUMMARY

The capillaries in the skin of the rabbit show an increase in permeability for approximately three hours after local application of xylene. This is indicated by the localization of trypan blue, india ink, antitoxins and vaccines virus in such areas. The skin may show all the cardinal features of inflammation, and still these substances may fail to localize and concentrate in the tissue. The period for which capillaries are more permeable may vary with different irritants. This is shown by the fact that trypan blue when given intravenously localizes and concentrates in areas of skin into which a 4 per cent sodium chloride solution was injected intradermally sixty minutes prior to injection of the dye. This same dye localizes and concentrates in the skin of the rabbit where horse serum is injected intradermally when the latter is given as long as twenty-four hours prior to intravenous injection of the dye.

The staphylococcus antitoxin used in this study was supplied by the Lederle Laboratories.

# RESECTION OF THE CARCINOMATOUS RECTO-SIGMOID JUNCTURE WITH REESTABLISHMENT OF INTESTINAL CONTINUITY

## SUBSEQUENT REPORT

HUBERT R. ARNOLD, M.D.

AND

J. FRANK SHEA, M.D.

SAN FRANCISCO

Since publication of the original article on this subject by one of us (H. R. A.), we have performed four more such operations, bringing the total to 5.

The reader is referred to the original article<sup>1</sup> for technic and illustrations of the procedure.

The second, third and fourth operations were carried out exactly as was originally described.<sup>1</sup> The second patient was operated on in December 1937. She was 68 years of age and well nourished. Her recovery was uneventful, and today she is well, with a normal anus, normal control of the bowel and no sign of recurrence. The third patient was a man 77 years of age and a poor surgical risk. He died on the tenth postoperative day as a result of gangrene of the distal portion of the sigmoid flexure with diffuse peritonitis. Gangrene was due to thrombosis of the blood supply to the distal portion of the sigmoid flexures, as was shown by autopsy. The fourth patient was operated on in June 1939. She made an uneventful recovery.

By further study of the blood supply we decided that the superior hemorrhoidal artery should be ligated at a point below the lowermost sigmoid branches since the portion of the sigmoid flexure remaining would be amply supplied by the sigmoid branches, and the part of the bowel supplied by the superior hemorrhoidal artery would be resected (fig. 1). By this means it would not be necessary to search for the so-called "critical point," and the sigmoid arterial branches would not be traumatized and therefore predisposed to thrombosis. In this manner the sigmoid arch of the blood vessels would not have to be preserved since the sigmoid branches would be left intact above the point of ligation of the superior hemorrhoidal artery. The sigmoid arteries supply the sigmoid flexure to the rectosigmoid juncture, and the sigmoid flexure is amputated 2 to 4 inches (5 to 10 cm.) above this point, together with

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<sup>1</sup> Arnold, H. R. Resection of the Carcinomatous Rectosigmoid Juncture. Arch Surg **38** 1004-1013 (June) 1939.

a large triangle of the mesocolon. Naturally, the middle hemorrhoidal arteries running in the lateral bands of the rectum are severed when this structure is cut. The inferior hemorrhoidal arteries by their anastomoses supply the stump of the rectum left after the portion of

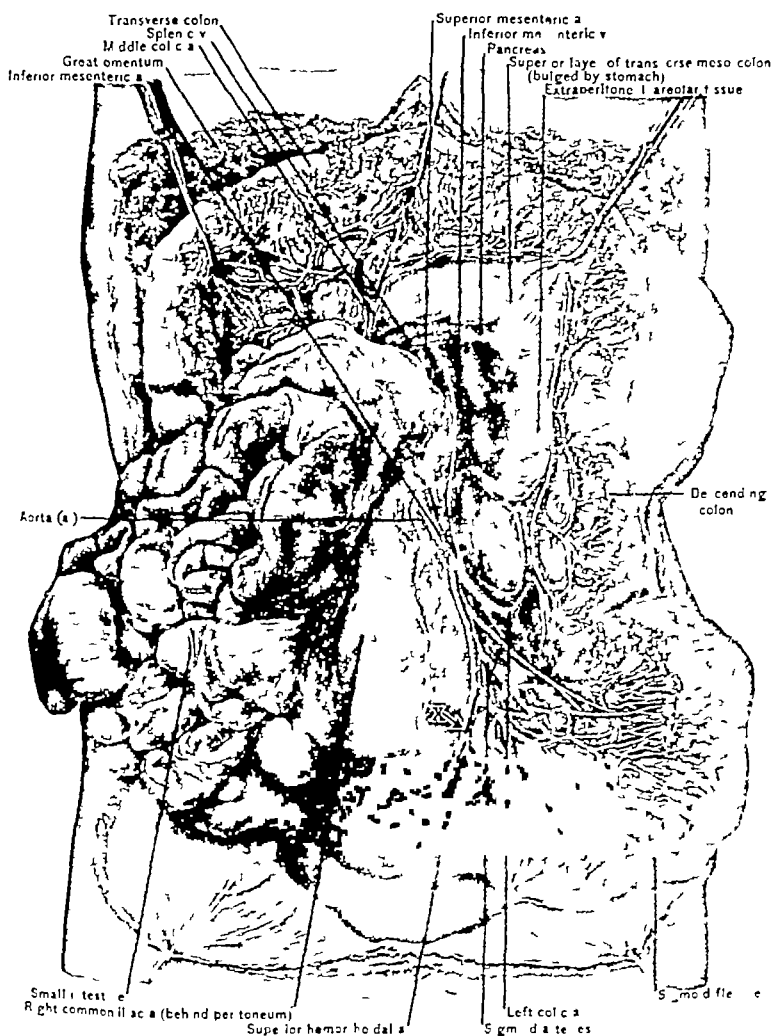


Fig 1—Illustration from Deaver's "Surgical Anatomy" (Philadelphia: P. Blakiston's Son & Co. 1901, vol 1). A indicates the point at which the superior hemorrhoidal artery is ligated below the sigmoid arteries.

bowel containing the rectosigmoid junction with the tumor is removed. Of course in some instances, as is shown in figure 2, it would be easy to ligate the superior hemorrhoidal artery above the lowermost sigmoid branch which forms the sigmoid arch, above the so called critical point or Hartmann.

## REPORT OF MOST RECENT CASE

The fifth and last patient operated on was treated by ligating the superior hemorrhoidal artery at a point below the lowermost sigmoid branches. He was a man 68 years of age and a very good surgical risk.

He was operated on Aug 18, 1939. His course was uneventful to the eighth postoperative day, when the upper part of the incision broke open. He was given 150 mg of procaine hydrochloride intraspinally, and the incision was cleaned. The bowels were distended, and therefore a cecostomy was done to decompress them. The abdomen was then closed without difficulty with retention sutures of silkworm gut and heavy chromic sutures. The wound healed per primam intentionem, and cecostomy worked excellently.

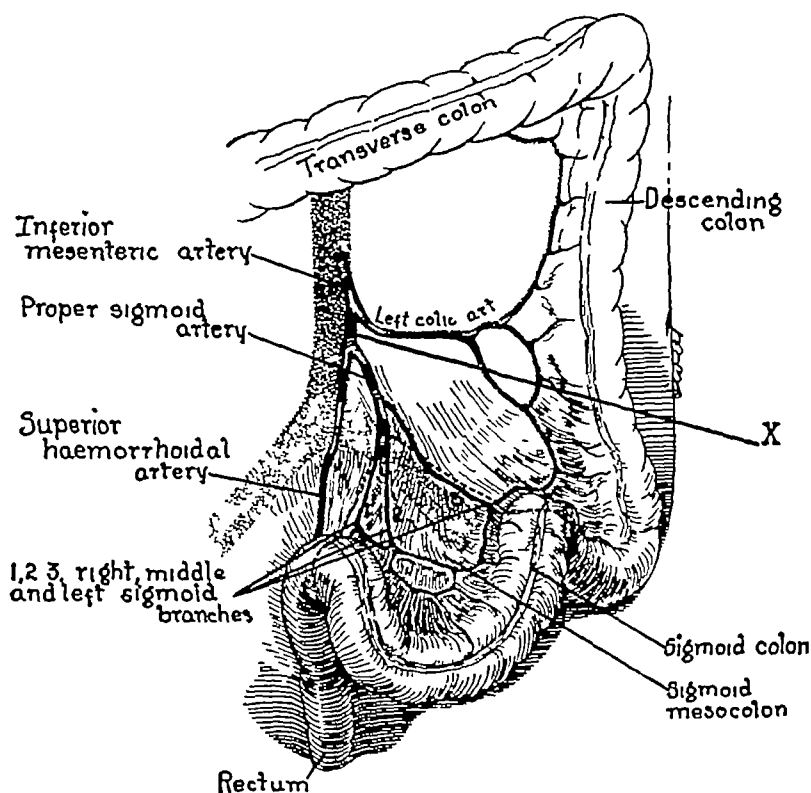


Fig 2—Sigmoid flexure of the colon and mesocolon, with special reference to the arterial supply. The arteries to the sigmoid flexure are the left (3), middle (2) and right (1) sigmoid arteries, which are branches from the inferior mesenteric artery, the large single branch of the inferior mesenteric artery is the superior hemorrhoidal artery, which supplies the upper part of the rectum. X indicates the point of ligation. Illustration from Callander's "Surgical Anatomy" (Philadelphia, W B Saunders Company, 1933).

Figure 3 shows the specimen removed at operation. Microscopic sections showed no metastatic nodules.

On the twelfth day after the original operation, clamps were applied to the septum in the double-barreled sacral colostomy, and these came off on the fourth day.

(It cannot be emphasized too strongly that the septum should be cut down to a depth of approximately 5 inches (127 cm). The usual right angle clamps have

too short a blade to crush the septum to this depth. When the first clamp sloughs out, it should be reapplied to crush the remainder of the septum if the septum has not been completely disposed of with the first crushing.)

The sacral colostomy opening closed spontaneously by November 15, and the cecostomy stoma was closed surgically with the region under local anesthesia two weeks later.

The rapid closing of the sacral colostomy stoma in this case was undoubtedly due to the presence of the cecostomy opening. However,



Fig 3 (case 5) —Specimen of the rectosigmoid junctione

the cecum should not be opened until the primary abdominal wound has been allowed to heal for several days.

There has been a heated debate in the literature over the spread of carcinoma in the distal part of the sigmoid flexure and in the rectosigmoid junction. The consensus at present is that downward spread is late and insignificant. Any one interested is referred to the voluminous literature on this subject. The operation described is not applicable to carcinoma of the rectal ampulla nor is it applicable to inoperable carcinoma in or above the rectosigmoid junction. It is hoped that by use of this procedure in cases of early operable carcinoma in this region patients will be given the benefit of normal control instead of an abdominal colostomy.

# EVALUATION OF THE INJECTION TREATMENT OF HERNIA IN OLDER PATIENTS

A THREE YEAR STATISTICAL ANALYSIS

LAZARUS MANOIL, M.D.

NEW YORK

The purpose of this paper is to present a brief analysis of cases of hernia treated by the injection method and to indicate the type of case in which this method of treatment is preferable. The consensus among surgeons is that operative measures are the best method of treating hernia. However, the management of older patients is always a problem, especially when another disease coexists. The high percentage of postoperative recurrence in such a group due to a variety of causes such as poor wound healing, infections and other complications, invites investigation of less hazardous procedures which promise relief. There is also a large group of younger patients who refuse operation because of fear, because of inability to meet the economic burden incurred or because they are unwilling to take "time off" for the operation. It is with these groups in mind, particularly the first, that study of the efficacy of the injection treatment was undertaken. Needless to say, this method has been enthusiastically recommended by many investigators.

The rationale of this method is to stimulate a high degree of fibroblastic proliferation firmly rooted in the surrounding defective muscle and fascia with as little inflammatory reaction as possible. If sufficient scar tissue can be produced to constrict the internal and external inguinal rings and partially obliterate the inguinal canal or its fascial plane, the end result may be similar to that obtained by operation except for removal of the sac. With the injection method, the sac remains empty, functionless and compressed by the surrounding proliferation of fibrous tissue. Therefore, not only is it unnecessary to obliterate the sac, but it is extremely dangerous to inject the sclerosing solution into it, because of the chemical peritonitis that will result. Healthy proliferation of scar tissue without pain or toxic effects was successfully produced with synasol (a 5 per cent solution of the sodium salts of certain of the fatty acids of the oil

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Presented before the Third Surgical Service of the Welfare Hospital, Dec 18, 1939

From the Hernia Clinic, the Surgical Service of Dr. J. Girsdansky, Gouverneur Hospital

extracted from a seed of the psyllium group) This has been demonstrated previously by a comparative histologic study of tissue response to other sclerosing solutions<sup>1</sup>

In addition to a safe and effective sclerosing solution, the use of a well fitting truss is essential It must be worn day and night during the course of injections, which takes six to eight weeks if given two or three times a week Thereafter the patient may remove the truss at night but must wear it during the day for four to six months My associates and I have used bilateral frame trusses in most of the cases reported in this series Since completion of this study, in February 1939, we have been prescribing only semielastic trusses These are more comfortable for steady wear, they hold the hernia reduced properly, and they cause little or no irritation of the skin, such as has occasionally occurred with the frame truss Continuous pressure to keep the hernia reduced during the course of treatment is very important, without it serious complications may result It is equally important that the patient cooperate in wearing the truss as instructed Two patients in our series were operated on for strangulation of the hernia because they removed their trusses at home against advice

The injection treatment of hernia, in my opinion, is particularly indicated for older patients who are considered poor surgical risks because of their age, their state of nutrition or other coexisting conditions It is also indicated for younger patients who refuse operation but are willing to cooperate in this treatment even though it is prolonged The best result may be expected in the case of a small inguinal hernia, but our series includes not only large indirect inguinal but direct inguinal, postoperative recurrent inguinal scrotal, femoral, umbilical and postoperative ventral types Most of these were of many years' duration All of them can be helped provided they are completely reducible and can be kept reduced with comfort during the course of treatment The patient is ambulatory, and the treatment does not interfere with his means of livelihood and other activities

The chief contraindication is an irreducible hernia This condition is very dangerous to treat by injections Patients who do not cooperate or cannot be fitted comfortably with a truss should not be treated by this method Sliding hernia and undescended testicles should be considered contraindicated Diabetes, syphilis, chronic bronchitis, asthma tuberculosis, prostatic disease and cardiac disorders are also considered contraindications by most observers, but in the hernia clinic we have not found them contraindicated

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<sup>1</sup> Manoil, L. Histologic Effects of Various Sclerosing Solutions Used in the Injection Treatment of Hernia, Arch Surg **36** 171-189 (Feb) 1938



## STATISTICAL STUDY

The data in the following tables are based on the study of 608 patients observed between February 1936 and February 1939. In 123 of these, 158 hernias were treated.

Table 1 shows the results in the cases in which the injection method was used. We arbitrarily considered as cured only those patients who continued to be symptomless without a truss for over six months after treatment. The period of treatment included the series of injections and a subsequent four to six month interval of truss support. In this group there were 19 hernias (12 per cent).

Patients who continued to wear their trusses six months after completion of treatment but who had no signs or symptoms of hernia were grouped as possibly cured. In this group there were 20 hernias (12.7 per cent).

TABLE 1—*Results of Injection Method*

Group A1 (cured without truss for over 6 months after treatment)	19, or 12%
Group A2 (possibly cured but still wearing truss 6 months after treatment)	20, or 12.7%
Group A3 (possibly cured and still wearing truss less than 6 months after treatment)	26, or 16.4%
Group A4 (possibly cured but not seen after 1 year of observation)	14, or 8.9%
Group B (clinically improved but not cured, includes those still under treatment)	48, or 30.4%
Group C (recurrences and failures)	26, or 16.4%
Group D (operated on after injection treatment)	5, or 3.2%
Total number of hernias	158

Patients who had no signs or symptoms of hernia and were still wearing their trusses less than six months after completion of treatment were grouped separately. In this group there were 26 hernias (16.4 per cent).

There was also a smaller group of patients without symptoms, some of whom discarded their trusses, while others continued to wear them but failed to reappear for examination after one year of observation. In this group there were 14 hernias (8.9 per cent).

In this table is included also a group of patients who after an adequate course of treatment still showed a slight impulse or slight bulging on straining but who were completely relieved of their subjective symptoms. These patients were definitely improved. Most of them continued to wear their trusses during the day. This group also included those still under treatment. In this group there were 48 hernias (30.4 per cent).

Recurrences and failures occurred with 26 hernias (16.4 per cent). The group represented by these includes patients who were clinically cured but who subsequently showed complete or partial recurrence. Many of these returned for continuation of injections. There was 1

patient whose hernia recurred three times after clinical cure by injection. There were 3 patients each of whom had two recurrences after treatment. In many of these cases recurrence or failure was unquestionably due to a poorly fitting or improperly worn truss, insufficient treatment or poor wound healing. This group also included patients who received more than six injections but did not complete the course of treatment.

Five patients (3.2 per cent) were operated on after the injection treatment, 2 because the hernia strangulated, 2 because the hernia recurred after injections and 1 because of impatience and dislike of the needle. There were no special difficulties at operation because of former injections.

TABLE 2—*Analysis of Patients Seen But Not Treated*

Waiting for trusses	33
Refusing any kind of treatment	35
Unable to get trusses	6
Unable to fit with trusses	3
Not cooperative	2
Not suitable for treatment	17
Did not return for treatment after given truss	221
Operation advised	96
No hernia found	37
Compensation cases	9
Not examined	0
Treated with adhesive strapping	1
Total	465

TABLE 3—*Types of Hernia Treated*

Indirect inguinal	68, or 43 %
Direct inguinal	45 or 28.5%
Recurrent inguinal	17, or 10.8%
Scrotal	22, or 14 %
Femoral	3 or 1.9%
Umbilical	1 or .6%
Postoperative ventral	2, or 1.2%
Bilateral inguinal	42 or 34.1%
Total	158

In table 2 are classified the large group of 465 patients who were seen at the clinic but were not given injection treatments. It is interesting to note that 221 patients in this group desired only the mechanical support of a truss, refusing operation or injection. Ninety-six younger patients were referred for operation.

Table 3 shows the types of hernia treated. Most of the hernias were large, and some had existed from forty to sixty years. Sixty-eight (43 per cent) were indirect inguinal, 45 (28.5 per cent) were direct inguinal and 17 (10.8 per cent) were recurrent inguinal hernias. Four of these were bilateral and recurrent, several had been operated on twice, with recurrence, and 1 had been operated on three times with recurrence.

There were also 22 scrotal hernias (14 per cent) of many years' duration. One patient had a bilateral femoral and 1 a recurrent femoral hernia. There was 1 female patient with an umbilical hernia 3 cm in

TABLE 4—*Analysis of Types of Hernia Classified in the Results of Each Group Treated*

Group A1 (cured without truss for over 6 months after treatment)	11 Indirect inguinal
	4 Direct inguinal
	1 Recurrent inguinal
	2 Scrotal
	1 Postoperative ventral
	—
	19
Group A2 (possibly cured but still wearing truss 6 months after treatment)	8 Indirect inguinal
	7 Direct inguinal
	5 Recurrent inguinal
	2 Scrotal
	—
	20
Group A3 (possibly cured less than 6 months after treatment and still wearing truss)	7 Indirect inguinal
	8 Direct inguinal
	2 Recurrent
	6 Scrotal
	2 Femoral
	1 Umbilical
	—
	26
Group A4 (possibly cured but not seen after 1 year of observation)	6 Indirect inguinal
	5 Direct inguinal
	3 Scrotal
	—
	14
Group B (clinically improved but not cured)	20 Indirect inguinal
	14 Direct inguinal
	6 Recurrent inguinal
	7 Scrotal
	1 Postoperative ventral
	—
	48
Group C (recurrences and failures)	13 Indirect inguinal
	8 Direct inguinal
	3 Recurrent inguinal
	2 Scrotal
	—
	26
Group D (operation after injection treatment)	3 Indirect inguinal
	1 Direct inguinal
	1 Femoral
	—
	5

diameter that was completely closed after 5 injections. Of the 2 post-operative ventral hernias, 1 followed a suprapubic prostatectomy and the other an appendectomy through a McBurney incision. It is interesting to note that there were 42 bilateral inguinal hernias (34.1 per cent) in this series of cases.

Table 5 shows the number of patients operated on in each group and the number of recurrences and failures in cases of hernia treated by injection. The incidence of recurrence and failure was about the same for indirect, direct and recurrent inguinal hernia. The percentage of failures for scrotal hernia was about half of those noted for the aforementioned types. Three indirect inguinal hernias, 1 direct inguinal hernia and 1 femoral hernia were operated on in this whole series.

Table 6 shows the percentage of recurrence in each age group. It is interesting to note here that 108 patients, or 92 per cent of the entire

TABLE 5—*Classification of Recurrences and Failures and Cases in Which Operation Was Performed for Each Type of Hernia*

Number of Hernias	Number and Per Cent of Recurrences and Failures	Number and Per Cent of Patients Operated On
68 indirect	13, or 19.1	3, or 4.4
45 direct	8 or 17.8	1, or 2.2
17 recurrent	3 or 17.7	0 0
22 scrotal	2 or 9.1	0 0
3 femoral	0 0	1 or 33.3
1 umbilical	0 0	0 0
2 postoperative	0 0	0 0

TABLE 6—*Analysis of Recurrence Rate in Each Age Group*

Age	Number of Patients	Number of Hernias	Recurrences	Per Cent
11-20	1	1	0	0
21-30	2	3	0	0
31-40	12	18	0	0
41-50	24	34	7	20.5
51-60	36	47	12	25.5
61-70	36	45	4	8.9
71-80	11	14	3	21.4
81-90	1	1	0	0

series, were between 41 and 90 years of age. There were 7 recurrences (20.5 per cent) among the 34 hernias in patients of the age group between 41 and 50. There were 12 recurrences (25.5 per cent) among the 47 hernias in patients of the age group from 51 to 60. There were 4 recurrences (8.9 per cent) among the 45 hernias in patients of the age group from 61 to 70. Lastly, there were 3 recurrences and failures (21.4 per cent) among 14 hernias in the patients between 71 and 80 years of age.

Table 7 shows the relation of the patient's age to the results of treatment. In the younger group of patients (between 11 and 40 years of age) there were no recurrences. Six after removal of the truss remained cured, 3 who were still wearing their trusses over six months after completion of treatment continued to be symptomless, 1 was pos-

sibly cured but was within the six month period since completion of treatment, 2 were possibly cured but were not seen after one year of observation following completion of treatment, and 4 were clinically improved or still under treatment. In the older group of patients between 41 and 90 years of age, there were 26 recurrences and failures (16.4 per cent), while 5 (3.2 per cent) were operated on. This totals 19.6 per cent of failures. Thirteen patients were cured and without truss support over six months after completion of treatment, 17 were still wearing their trusses over six months after completion of treatment but continued to be symptomless, 25 were possibly cured but were within the six month period since completion of treatment, 12 were possibly cured but were not seen after one year of observation following completion of treatment, and 43 were clinically improved or still under treatment.

TABLE 7—*Analysis of Results in Relation to Age of Patients*

Age	Group *						
	A1	A2	A3	A4	B	C	D
11-20	1	0	0	0	0	0	0
21-30	2	0	0	0	1	0	0
31-40	3	3	1	2	4	0	0
41-50	4	7	6	3	6	7	1
51-60	3	5	5	4	15	12	4
61-70	4	5	10	4	17	4	0
71-80	2	0	4	1	4	3	0
81-90	0	0	0	0	1	0	0
	19(12%)	20(12.7%)	26(16.4%)	14(8.9%)	48(30.4%)	26(16.4%)	5(3.2%)

\* For explanation of groups, see table 1

Complications were comparatively few during the last eighteen months of the study, owing to improvement of technic. Altogether, during the entire three year period, there were eight swellings of the cord, which subsided in two or three weeks, and twenty-two peritoneal reactions characterized by local or general abdominal pain. These reactions usually cleared up within one to three hours. There were 2 cases of strangulation, as has been noted. No cases of atrophy of the testes or sexual impotence were noted. There were no infections and no mortalities.

#### COMMENT

The reports in the literature in the past ten years on the injection treatment of hernia, by Fowler,<sup>2</sup> Rice,<sup>3</sup> and Bratrud<sup>4</sup> of the Minneapolis

2 Fowler, S. W. Experience with the Injection Treatment of Hernia, *M Rec* **101** 207-209 (Feb 20) 1935

3 Rice, C. O. The Injection Treatment of Hernia. Evaluation of Technic and Results, *Ann Surg* **105** 343-351 (March) 1937

4 Bratrud, A. F. Ambulant Treatment of Hernia, *Journal-Lancet* **54** 337-341 (June 15) 1934

General Hospital, McKinney<sup>7</sup> of the University of Minnesota, McMillan and Cunningham<sup>8</sup> from the department of surgery of the Northwestern Medical School, Crohn<sup>9</sup> of the Michael Reese Hospital Chicago, Harris and White<sup>8</sup> of San Francisco and many others, show invariably a high percentage of cures in well selected cases of hernia treated by the injection method. The only report of extremely discouraging results made after a two year study of only 66 cases was that of Burdick and Coley<sup>9</sup> of the Hospital for the Ruptured and Crippled New York. From a three year statistical study of 123 patients with 158 hernias, my associates and I were convinced that the results do not indicate a large percentage of cures but do indicate an excellent palliative result in a large number of cases. It must be borne in mind that 92 per cent of the patients treated were between 41 and 90 years of age with large hernias of long duration, many of whom would have been considered poor surgical risks. There is no doubt that many of these patients would have continued to be uncomfortable with or without a truss if they had not been given the injection treatment. Most of them have been satisfied with the result, and many have been able to return to some type of work. Patients with recurrence after injection treatment were given a subsequent series of injections to secure firm closure of the hernia. The hernias that failed to close improved sufficiently to enable the patient to wear a truss comfortably and to maintain the hernia in complete reduction. In the small group of 15 younger patients (between the ages of 11 and 40) no recurrences have been noted to date. One might infer from this that the injection method compares favorably with operation for younger patients. I reiterate that the injection method is the method of choice for older patients, for reasons already mentioned.

Wangensteen<sup>10</sup> stated

It is not without significance that not one patient of several hundred treated by the injection method in the 2 surgical clinics (U of Minnesota, and Minneapolis General Hospital) has died as a direct result of this treatment. As much can

5 McKinney, F S. An Evaluation of the Results of the Injection Treatment of Inguinal Hernia. Review of Employment of This Method at University of Minnesota Hospital, *Ann Surg* **105** 338-343 (March) 1937.

6 McMillan, W M, and Cunningham, D R. The Injection Treatment of Reducible Hernia, *J A M A* **106** 1791-1795 (May 23) 1936.

7 Crohn, N N. The Injection Treatment of Hernia *J A M A* **108** 540-544 (Feb 13) 1937.

8 Harris, F I, and White A S. Evaluation of the Injection Treatment of Hernia, *J A M A* **111** 2009-2013 (Nov 26) 1938.

9 Burdick C G and Coley B L. Injection Method of Treating Hernia *Ann Surg* **106** 322-333 (Sept) 1937.

10 Wangenstein, O H. The Status of the Injection Treatment of Hernia *Ann Surg* **105** 322-324 (March) 1937.

rarely be said for large series of similar size treated by operation. This method of treating selected cases of hernia has merit and when skillfully employed would appear to carry little risk of serious complication.

He continued

Medicine has come to recognize the superiority of trial over reason. Rationalizations concerning the merits of a method are likely to lead to error, not so much because the logic employed is poor but more often because the initial premise itself is false. The injection treatment of hernia is not therefore to be dismissed without examination. The rejection of obliteration of hemorrhoidal varicosities and varicose veins of the lower extremities by injection is fresh enough in the recollection of medical men to remind them that the prejudices cannot delay the march of progress.

#### SUMMARY AND CONCLUSIONS

The injection method of treating hernia has many advocates. Many clinics here and abroad have been giving it ever increasing attention. The importance of the principles to be observed in the management of hernia as originally stated by Billroth, and affirmed more recently by Bratrud, Rice, Wangenstein and others, cannot be overemphasized. These principles are the use of a safe and effective sclerosing solution, a satisfactory truss, knowledge of the regional anatomy and full cooperation of the patient.

During the period between February 1936 and February 1939, 158 hernias in 123 patients were treated by the injection method at this clinic. Ninety-two per cent of these patients were between 41 and 90 years of age. Recurrence took place in 26, or 16.4 per cent, of this group, and 5 patients, or 3.2 per cent, were operated on after injection, making a total percentage of failures of 19.6 per cent. In the 15 younger patients between 11 and 40 years of age there were no recurrences. There were no infections and no mortality. The injection treatment is the method of choice for older patients provided the hernia is reducible and can be comfortably maintained with a truss. It should be the alternative method of treatment for younger patients who refuse operation.

# PATHOLOGY OF SHOCK IN MAN

## VISCERAL EFFECTS OF TRAUMA, HEMORRHAGE, BURNS AND SURGICAL OPERATIONS

HARRY A DAVIS, M D

NEW ORLEANS

Present knowledge of the syndrome of shock in man rests largely on physiologic investigations in lower animals. Studies of pathologic changes are decidedly more limited, and Moon and Kennedy<sup>1</sup> deserve much credit for drawing attention to the importance of these alterations.

The present study is concerned with the visceral changes present in 50 patients who died in a state clinically diagnosed as shock and on whom postmortem examinations were performed from one to three hours later. An effort has been made to demonstrate that definite alterations occur in the viscera as the result of shock and that the character of these changes is dependent on the etiologic factors involved. The changes are grouped according to the clinical states from which they arose, and their significance is briefly discussed. These states include

- 1 Cerebral trauma—10 cases
  - A Early death
  - B Delayed death
- 2 Trauma to the abdomen, thorax or extremities—31 cases
  - A Early death with
    - (a) Open hemorrhage
    - (b) Closed hemorrhage
    - (c) Regional segregation of blood
    - (d) Infection
  - B Delayed death
- 3 Trauma following burns—5 cases
  - A Early death
  - B Delayed death
- 4 Trauma following surgical procedures—4 cases

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From the Department of Pathology of the University of Tennessee School of Medicine and the Department of Surgery of the School of Medicine of Louisiana State University

<sup>1</sup> Moon V H and Kennedy P J Pathology of Shock Arch Path **14**  
360 371 (Sept ) 1932



## CEREBRAL TRAUMA

In this group of 10 cases trauma resulted either from a gunshot wound or from direct contusion with a blunt instrument. In the majority of instances death occurred within eighteen hours and was most rapid after gunshot injuries.

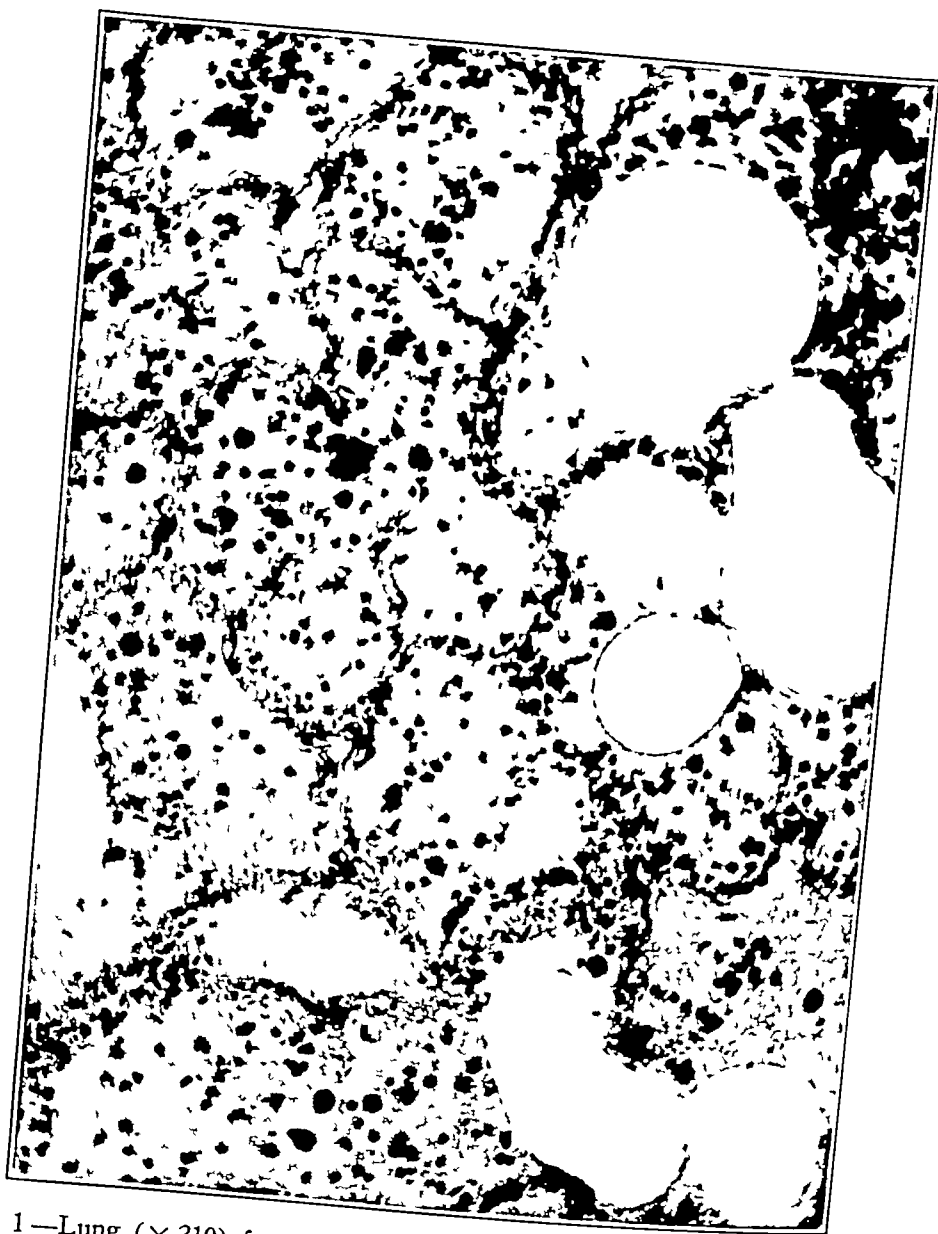


Fig 1—Lung ( $\times 210$ ) from a case of cerebral trauma with early death. Note pulmonary edema, congestion of the alveolar capillaries and diapedesis of erythrocytes into the alveoli. Many "heart failure" cells are present.

In fatal cases of cerebral trauma there is present a dilatation which is probably generalized in character but which is manifested at autopsy chiefly as a vascular congestion of the lungs and the abdominal viscera. This dilatation would seem to be dependent on failure of the vasomotor

center, which in turn follows prolonged oxygen deficiency. Edema of the lungs, with diapedesis of red blood cells into the alveolar spaces, and numerous macrophage cells containing iron pigment are also more or less constant findings (fig 1)

It should be pointed out that it is impossible to exclude as a factor in the production of the pathologic picture the effect of cardiac failure

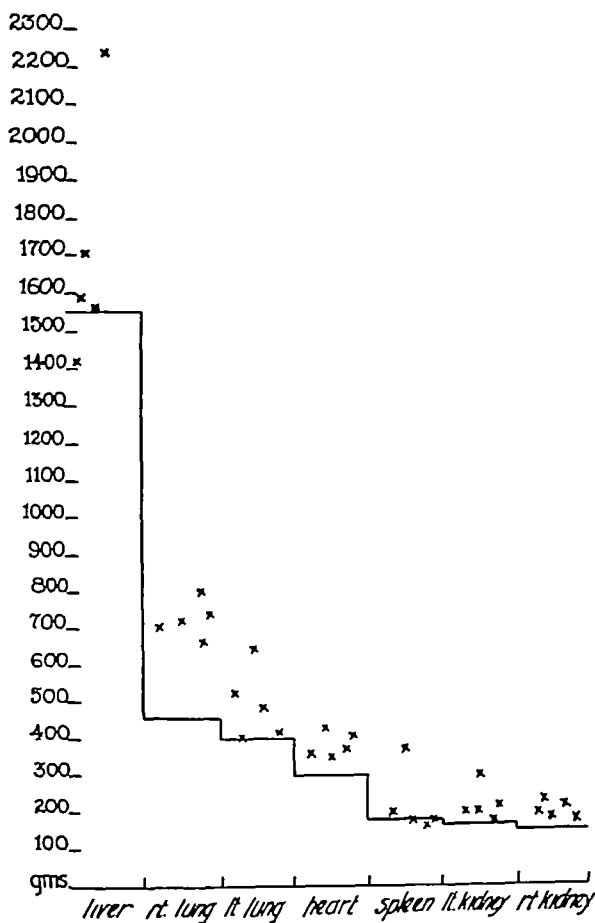


Fig 2—Distribution of visceral weights in 5 cases of cerebral trauma with early death

with progressive diminution of the cardiac output. It is suggested that any condition which leads to anoxemia of the central nervous system would seem to be capable of producing similar pathologic changes. It is also suggested that the pathologic picture is necessarily dependent on the total circulating blood volume at the time of death. Reduction of the blood volume, whether by open or by closed hemorrhage, tends to obscure the presence of a terminal vasodilatation. The presence of

pulmonary edema even in patients to whom fluids have not been administered intravenously suggests that an altered permeability of the pulmonary capillaries occurs

A study of the viscera in this group of patients revealed a definite increase in weight due to the distention of the blood vessels with blood (fig 2)

The available facts would seem to point, therefore, toward two processes at work in the production of the visceral pathologic changes fol-

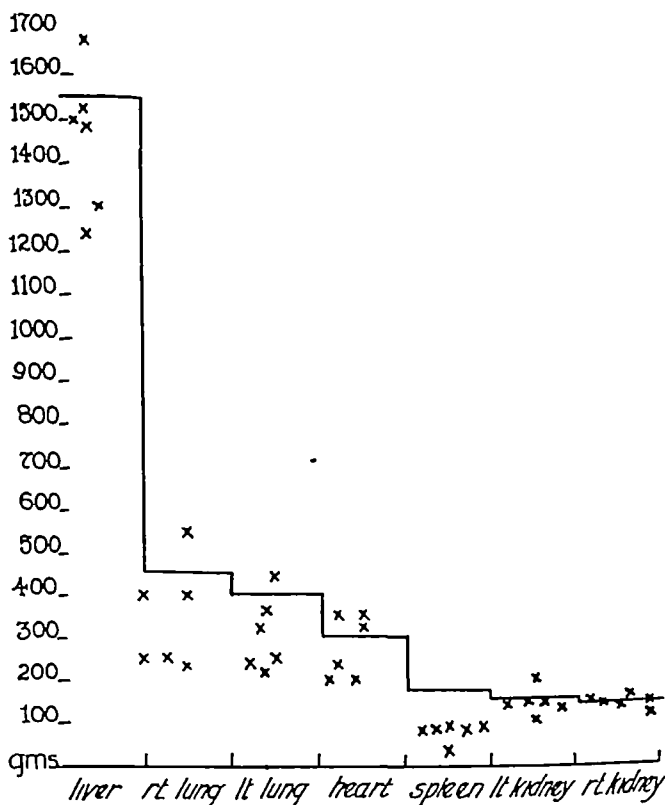


Fig 3—Distribution of visceral weights in 6 cases of trauma to the abdomen, thorax or extremities with open hemorrhage and early death

lowing cerebral trauma (1) a vasodilatation in the splanchnic and thoracic areas and (2) cardiac failure. The time factor is of great importance here. When cerebral compression occurs very rapidly and death also occurs quickly, extreme thoracic and splanchnic vasodilatation is found. When cerebral compression is more gradual and death slower, the central vasodilatation, although still present, is less marked. A similar type of vasodilatation has been produced experimentally in dogs by either rapid or gradual increase in intracranial pressure (Davis<sup>2</sup>). It has also been reported following cerebral edema (Ala-

2 Davis, H. A. Unpublished data

jouanine and Horner<sup>3</sup>) and traumatic lesions of the brain stem (Wanke<sup>4</sup>) Blalock<sup>5</sup> has pointed out that in experimental cerebral trauma a diminution of cardiac output occurs simultaneously with a reduction in blood pressure

#### TRAUMA TO THE THORAX, ABDOMEN OR EXTREMITIES

Before discussing the group of 31 cases in which death occurred promptly after trauma to the abdomen, thorax or extremities, it is necessary to define the terms "open hemorrhage" and "closed hemorrhage" In the sense intended here, the term "open hemorrhage" means free hemorrhage into an open cavity, such as the peritoneal or pleural cavities, or external bleeding Closed hemorrhage signifies hemorrhage into tissues which prevent its escape externally or into an open cavity Retroperitoneal hemorrhage, intramesenteric hemorrhage and intramuscular hemorrhage are all instances of the closed variety The distinction between open and closed hemorrhage is of great importance in the interpretation of the pathologic changes in shock in relation to the administration of fluids Those cases in which death occurred within forty-eight hours of the receipt of the injury were grouped as early deaths Those in which death occurred after forty-eight hours were considered as delayed deaths This grouping is entirely arbitrary

*Early Death from Open Hemorrhage*—To speak generally, in this group of cases the amount of free blood varied from 900 to 2,200 cc The heart revealed no pathologic change other than marked contraction The spleen was also markedly contracted The liver was usually pale and anemic, and the weight was normal or subnormal The liver cells were usually swollen, and the liver capillaries were empty The kidneys had a tendency to be reduced in weight and usually were pale and dry in appearance The epithelium of the convoluted tubules showed varying degrees of parenchymatous degeneration The visceral weights were decreased (fig 3)

The changes in the lungs were interesting The weight, as a rule, was below normal, but the longer the duration of the shock the heavier were the lungs The color was pale, and there was no evidence of petechial hemorrhages Varying degrees of emphysema were observed on microscopic examination There was moderate congestion of the alveolar capillaries, with moderately frequent collections of "heart

3 Alajouanine T and Horner, T L'edeme cerebral generalise (etude anatomique) *Ann d'anat path.* **16** 133-163 (Feb) 1939

4 Wanke R Zum Nachweis und zur Auswirkung der traumatischen Hirnstaumlaesion *Arch f klin Chir* **193** 676-701 1938

5 Blalock, A and Bradburn H B Trauma to Central Nervous System Its Effects on Cardiac Output and Blood Pressure Experimental Study, *Arch Surg* **19** 725-734 (Oct) 1929

failure" cells (fig 4) Pulmonary edema was not usually present, particularly in those patients who died within twelve to eighteen hours after admission to the hospital When present, it was patchy in character No diapedesis of red blood cells into the alveolar spaces was



Fig 4—Lung ( $\times 210$ ) from a case of trauma to the abdomen with open hemorrhage into the peritoneal cavity and early death Note congestion of the alveolar capillaries and "heart failure" cells lying in the alveolar spaces

observed Since fluids were administered by the intravenous route to nearly all these patients, the relatively minimal pulmonary edema observed needs some explanation

*Early Death with Closed Hemorrhage*—In this group of 5 cases the pathologic features resembled those seen in patients dying from open

hemorrhage with one exception, that the lungs showed edema, with red blood cells and "heart failure" cells in the alveolar spaces (fig 5). The distribution of visceral weights in this group is shown in figure 6.

In fatal open hemorrhage the visceral changes are similar to those seen in closed hemorrhage except for the pulmonary edema which is



Fig 5—Lung ( $\times 210$ ) from a case of trauma to the abdomen with closed hemorrhage into the retroperitoneal tissues and early death. Note pulmonary edema, congestion of the alveolar capillaries and heart failure cells.

associated with the closed variety. Macrophage cells containing iron pigment are present in the alveoli in both types of hemorrhage but are more numerous in the closed type.

What explanation can be offered for this dissimilarity in the pulmonary observations especially since both groups of patients have been given fluids intravenously? The difference may be explainable on the basis of an anoxemia of the central nervous system. The pathologic picture of anoxemia of the brain resulting from a rapid increase of intracranial pressure includes pulmonary congestion and edema. Such an anoxemia may result, however, from a reduction of the total blood volume. The rate of the reduction of the volume of blood must be considered in this connection. When the bleeding is rapid, as in an open type of hemorrhage death takes place too rapidly to permit the

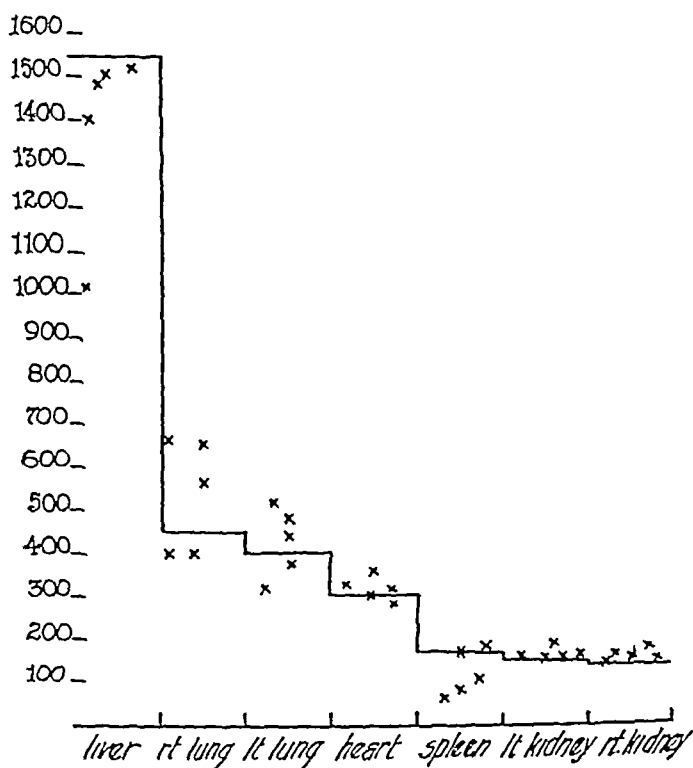


Fig 6—Distribution of visceral weights in 5 cases of trauma to the abdomen, thorax or extremities with closed hemorrhage and early death

full effects of anoxemia of the nervous system to develop. When, on the other hand, the rate of bleeding is slower, as in the closed form of hemorrhage, anoxemia of the central nervous system is of longer duration and becomes more apparent in its effects on the viscera. This may explain the presence of pulmonary edema, which forms part of the pathologic picture associated with anoxemia of the brain in the closed form of hemorrhage. It may explain, also, the pulmonary edema and vascular congestion of the viscera which occur in those patients who die with either open or closed hemorrhage after forty-eight hours. In such patients the anoxemia of the central nervous system has been

prolonged enough to produce an effect on the vascular bed of the viscera. It becomes apparent from this discussion that any agent which reduces the effective and/or total blood volume may produce thereby an anoxemia of the central nervous system and its resultant pathologic picture of pulmonary edema and congestion with visceral vascular congestion. When the blood volume is much reduced, the presence of these visceral vascular changes may be hidden.

*Early Death with Segregation of Blood*—In three of the 50 cases the estimated loss of blood from the circulation was insufficient to explain the fatal outcome. Examination, however, always revealed the presence of a segregation of blood in some part of the venous system as a result of the mechanical pressure of a collection of blood at some strategic point. Such a situation develops, for instance, when hemo-pericardium develops following a cardiac wound or when a retroperitoneal hemorrhage compresses the inferior vena cava. Hepler and Simonds<sup>6</sup> have also emphasized the importance of a segregation of blood in the production of shock. The pathologic change associated with a regional segregation of blood is a vascular congestion of the viscera below the point of venous obstruction. It should be pointed out again that in this group of cases the usual anatomic changes of hemorrhage are not found. Congestion of the spleen and edema of the lung (fig 7) were constant additional findings. The diminution of cardiac output associated with the segregation of blood in the venous side of the circulation leads to anoxemia of the central nervous system, and this, in turn, accentuates the vascular distention of the viscera. The visceral weights were always increased (fig 8). The clinical recognition of the occurrence of a regional segregation of blood is most important, inasmuch as the administration of fluids to such patients is definitely harmful, for it increases the rate of circulation and therefore forces the blood more rapidly into the segregated area.

*Early Death with Infection*—Only 1 of the 50 patients in this series came under this heading. In this patient death resulted from a *Clostridium welchii* infection of the area of traumatized muscle of the abdominal wall after a gunshot wound. The essential features of the case were mild hemoconcentration, widespread vascular congestion of the viscera and hemolysis, as evidenced by the large amounts of iron pigment in the spleen, liver and lungs. Such an infection is liable to complicate a gunshot wound of the abdomen when the bullet has perforated the bowel wall and then lodged in the abdominal musculature.

<sup>6</sup> Hepler, O. E. and Simonds, J. P. Mechanism of Shock. Effects of Intravenous Injection of Salt Solution in Collapse Induced by Mechanical Impounding of Splanchnic Region in Normal and Hyperthyroid Dogs. Arch. Path. 25: 149-159 (Feb.) 1938.





Fig 7—Lung ( $\times 210$ ) from a case of trauma to the thorax, with regional segregation of blood and early death. Note pulmonary edema, congestion of the alveolar capillaries, diapedesis of erythrocytes and "heart failure" cells.

It is well known that such an infection may be fulminating in character and that death may occur as early as seven hours after the injury. It is important, therefore, that this possibility be borne in mind and that appropriate cultures be taken after death from the site of trauma. Such cultures sometimes reveal the presence of this group of organisms.

The fulminating infection may be accompanied by symptoms which closely resemble those of shock. The general pathologic changes are

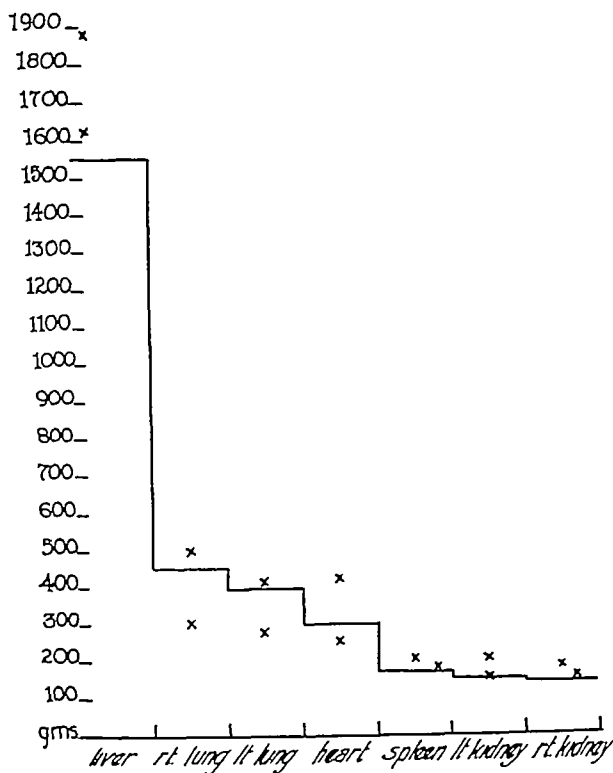


Fig 8—Distribution of visceral weights in 2 cases of trauma to the abdomen, thorax or extremities with regional segregation of blood and early death.

intense congestion of the vascular bed, with increased vascular permeability. There is marked hemolysis, and iron-containing pigment is deposited in the lungs, liver and spleen. The liver may show fatty metamorphosis, but may not if death occurs very rapidly. The lungs are edematous and extremely congested. The blood picture, as in the case reported, reveals hemoconcentration and leukocytosis. It seems likely that some cases of this type have not heretofore been recognized as resulting from such infections and perhaps have been used as presumptive evidence to support the toxic theory of traumatic shock.

*Delayed Death with Open or Closed Hemorrhage*—There were 9 patients whose deaths occurred more than forty-eight hours from the time of injury. In every case evidences of infection were present, though the form varied. There were no anatomic evidences of open hemorrhage, and extreme splenic contraction was not usually present.

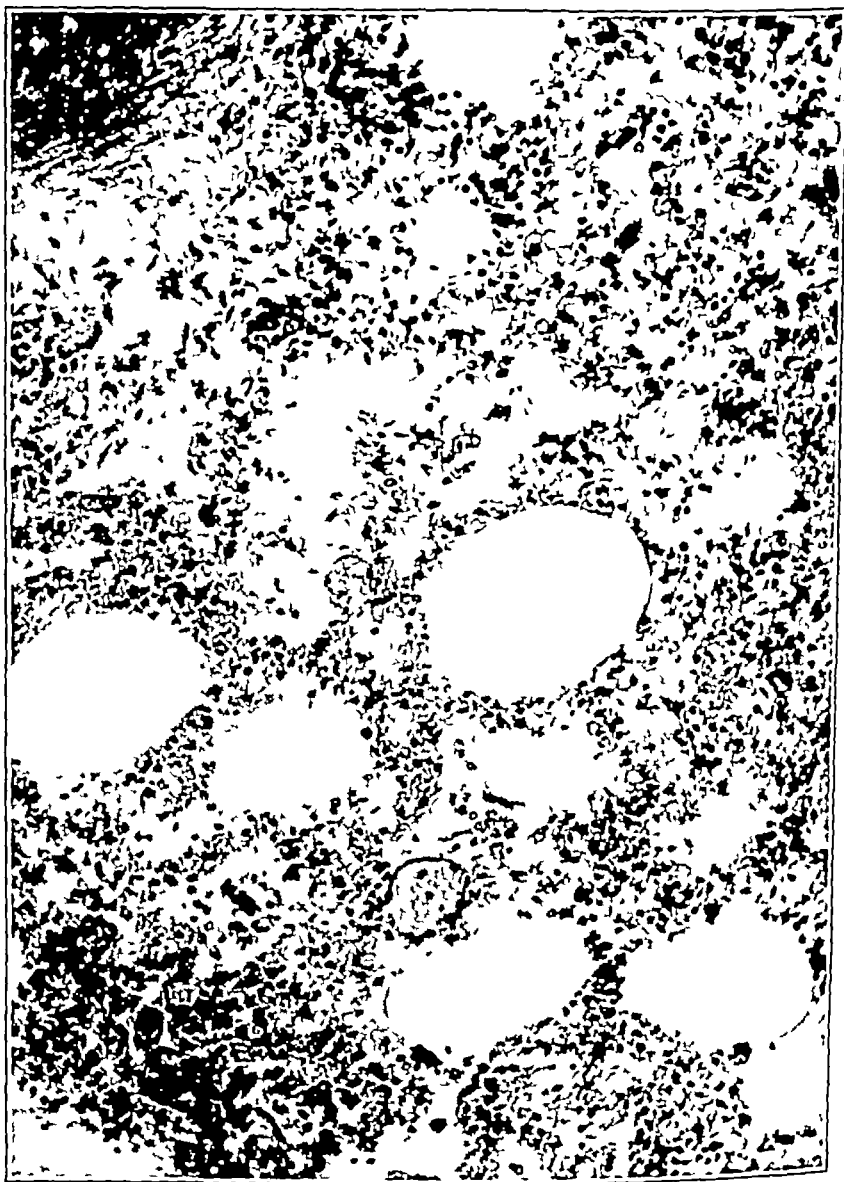


Fig 9—Lung ( $\times 210$ ) from a case of trauma to the abdomen with slow open hemorrhage and delayed death. Note pulmonary edema, congestion of the alveolar capillaries and "heart failure" cells.

In many cases the pathologic changes associated with early peritonitis were observed.

Pulmonary edema was, on the whole, more marked in the group whose deaths were delayed than in the group whose deaths occurred

earlier (fig 9) In most patients a peculiar type of pneumonia was present, which varied greatly in extent The edema present was patchy The alveoli in certain areas were filled with only a pink-staining fluid with a variable admixture of large mononuclear cells containing an iron pigment In other alveoli and bronchi the pink-staining fluid had been invaded by numerous polymorphonuclear leukocytes and evidences of

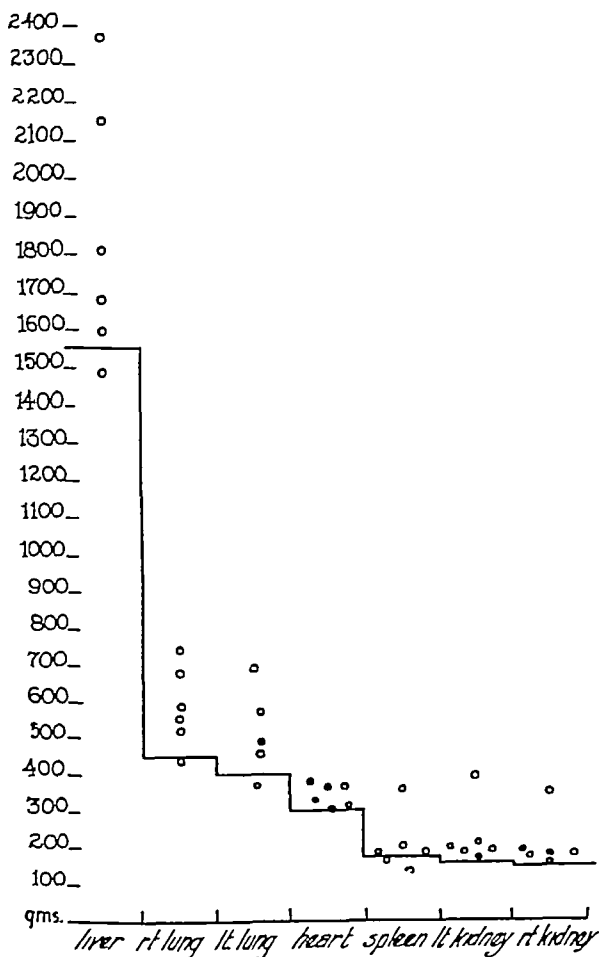


Fig 10—Distribution of visceral weights in 6 cases of trauma to the abdomen thorax or extremities with open hemorrhage and delayed death

fibrin formation were present Many pigment-containing mononuclear cells lay side by side in the alveoli with polymorphonuclear leukocytes Congestion of the alveolar capillaries was extreme

Another histologic feature of interest was observed in these cases of delayed death an apparently increased breakdown of the red blood cells This was most marked in the spleen in which much iron-containing pigment was found free in the tissues or lying within the large

mononuclear cells. Iron-containing pigment was also present in increased amounts within the mononuclear cells of the lungs and in the Kupffer cells of the liver. The increased hemolysis was noted in patients with open as well as in patients with closed hemorrhage. It was not dependent on the presence of infection, but when it was associated with it the degree of erythrocytic destruction was increased, particularly when the infection was due to *Cl. welchii* and related organisms. The distribution of visceral weights in this group is illustrated in figure 10.

The importance of the time factor in the production of the visceral changes is clearly illustrated in cases of thoracic and abdominal injuries in which death is delayed. The visceral anemia and splenic contraction present in the early stages of shock give place, when death is deferred to vascular congestion and increase in weight of the viscera. Pulmonary edema also becomes more evident, as do the signs of increased destruction of red blood cells, and large amounts of iron pigment may be seen in the lungs, the liver and, in particular, the spleen.

Several factors must be taken into consideration when these changes are discussed. Three of these considerations seem to be especially important. 1. With the longer duration of life there is likely to be a larger administration of intravenous fluids. 2. Infection, variable in degree, is likely to supervene. 3. Prolonged low blood pressure is likely to lead to anoxemia of the central nervous system with resulting visceral vasodilatation and an alteration in the permeability of the capillaries, particularly the pulmonary capillaries.

It is essential to recognize the important role played by anoxemia of the central nervous system in the production of visceral vasodilatation and pulmonary changes. This factor it should be emphasized, is present in every form of shock, though its effects may be masked if an extreme reduction of blood volume occurs before death.

#### TRAUMA DUE TO BURNS

The visceral changes present in early and late deaths from thermal trauma need not be discussed in any great detail. Patients who die soon after their injuries usually reveal a diminution of the weights of the various viscera (fig. 11), contraction of the spleen and other evidences of a rapid reduction of the total blood volume. Fatty metamorphosis of the liver, widespread petechial hemorrhages and other signs suggestive of the presence of a circulating toxin are sometimes observed in patients who die as early as five hours after the receipt of the burn.

When death is delayed after burns, evidences are found of widespread vascular congestion, an increase in the visceral weights (fig. 11), an absence of splenic contraction, widespread petechial hemorrhages and marked pulmonary edema. There is also present an excessive destruc-

tion of red blood cells, associated with the presence of large amounts of iron-containing pigment in the spleen, liver and lungs. Whether the hemolysis is due to the action of a circulating toxin or to excessive activity of the reticuloendothelial system cannot be stated definitely at this time. We have not found necrosis of the liver, which has been noted by various observers, e g, Belt,<sup>7</sup> although fatty metamorphosis of the liver is a frequent finding.

Considerable discussion has arisen as to the cause of the hypotension associated with trauma due to burns. One group of observers has

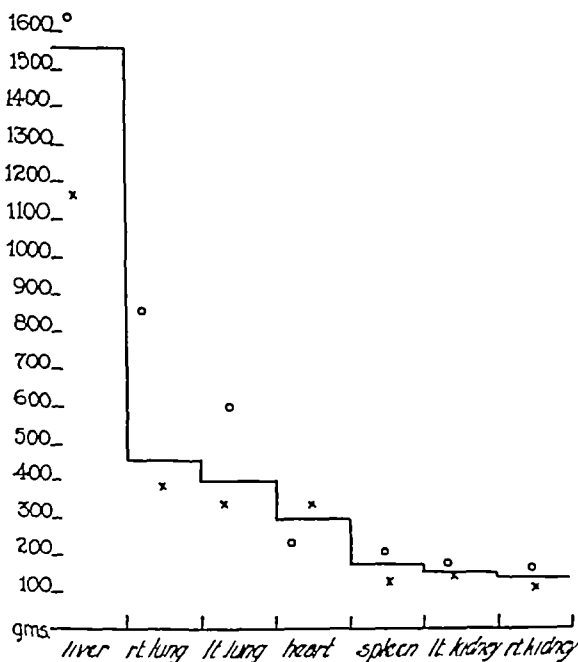


Fig. 11—Distribution of visceral weights in 2 cases of burns. x = early death  
o = delayed death

described a major role to the toxins released from the burned area (Bardden<sup>8</sup>). A second group has held that the fall is due to a shift of fluid into the burned area (Underhill and co-workers,<sup>9</sup> Harkins<sup>10</sup>). Still

<sup>7</sup> Belt T. H. Liver Necrosis Following Burns Simulating the Lesions of Yellow Fever. *J. Path. & Bact.* **48**: 493-498 (May) 1919.

<sup>8</sup> Bardden C. R. A Review of the Pathology of Superficial Burns with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns. *Johns Hopkins Hosp. Rep.* **7**: 137-179 (1898).

<sup>9</sup> Underhill F. P., Carrington G. I., Kapsnow K. and Peck G. T. H. Concentrations in Extensive Superficial Burns and Their Significance for Systemic Treatment. *Arch. Int. Med.* **32**: 31-49 (July) 1925.

<sup>10</sup> Harkins H. N. Experimental Burns. I. Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burn. *Arch. Surg.* **31**: 71-87 (July) 1920.

another group has maintained that the early fall in blood pressure is due to loss of fluid into the traumatized area and that later hypotension is due to a toxemia (Wilson and co-workers<sup>11</sup>). The argument is still unsettled.

#### TRAUMA DUE TO OPERATION

Numerous factors are involved in the syndrome of shock following surgical procedures. I have excluded from this series such complications as postoperative infections, pulmonary embolism and similar conditions. This process of exclusion leaves 4 cases which are grouped under the heading of shock due to operative trauma.

In the fatalities following surgical procedures within the abdomen in this series, shock was always associated with marked vascular congestion of the splanchnic area. The organs were increased in weight and the spleen was congested (fig. 12). As has been pointed out, vasoconstriction of the splanchnic area normally follows a reduction of blood volume (Davis and Jermstad<sup>12</sup>) but in these cases in spite of large losses of blood this did not occur. Instead a vasodilation was present which, in fact, might have resulted from the direct trauma of the intra-abdominal operation. The significance of anesthesia, particularly of spinal anesthesia, must also be considered in the production of these vascular changes.

The extent of the vasodilatation is difficult to determine. In operations within the peritoneal cavity, it is chiefly confined to the splanchnic area. The lungs are only moderately congested and pulmonary edema is not a conspicuous or a constant feature. In the particular group of cases under discussion the phenomena of vasodilatation were always accompanied by open or by closed hemorrhage but the amount of blood lost was not in itself sufficient to cause death if a normally reacting splanchnic vascular bed had been present. A compensatory splanchnic vasoconstriction, however, had not occurred in these cases. It is therefore apparent that in postoperative shock one is confronted by two phenomena: vasodilatation of varying degrees and a reduction of the blood volume. The combination of these phenomena accentuates the state of shock.

At this point it is possible to sum up as follows the factors which influence visceral changes in patients dying from shock due to various forms of trauma:

- 1 The site of the trauma, e. g., whether to the central nervous system, the abdomen, the thorax or other organs.
- 2 The mode of production of the trauma, e. g., by a bullet wound or a surgical operation.

11 Wilson, W. C., Jeffrey, J. S., Roxburgh, A. N., and Stewart, C. P. Toxin Formation in Burned Tissues, *Brit. J. Surg.* **24**: 601-611 (Jan.) 1937.

12 Davis, H. A., and Jermstad, R. J. Regional Distribution of Blood in Experimental Secondary Shock, *Arch. Surg.* **38**: 556-580 (March) 1939.

- 3 The rate of reduction of the effective and/or total blood volume
- 4 The duration of shock
- 5 The total blood volume at the time of death
- 6 The presence or absence of a regional segregation of blood
- 7 The mechanism of production of shock by vasodilatation as in cerebral injuries and surgical operations, or by reduction of the blood volume, as in open or closed hemorrhage

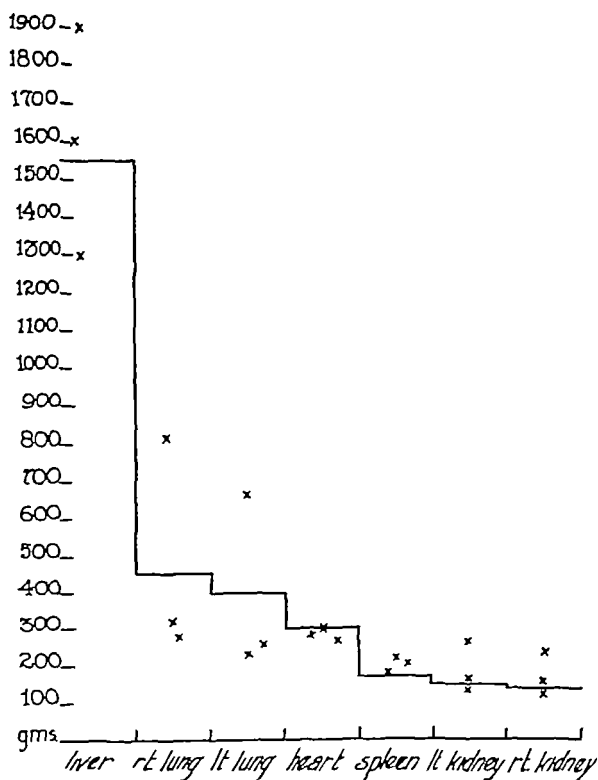


Fig 12—Distribution of visceral weights in 3 cases of trauma following surgical procedures

8 The presence of a circulating toxin, as in burns or in fulminating gas bacillus infections

9 The intravenous administration of fluids

Finally, it might be pertinent to discuss the significance of certain less common pathologic changes. Some emphasis has been placed on the frequent presence of subendocardial hemorrhage in patients dying from obstetric shock (Sheehan<sup>13</sup>). Such hemorrhages have also been found in patients dying from burns (Bardeen<sup>5</sup>), from gunshot wounds

<sup>13</sup> Sheehan H. L. The Pathology of Obstetric Shock. J Obst & Gynaec Brit Emp 46 218-231 (April) 1939



(Moon and Kennedy,<sup>1</sup> Kulbs and Strauss<sup>14</sup>) and from cerebral injuries of various types (Sheehan<sup>15</sup>) In this series the presence of subendocardial hemorrhages has been noted in 3 patients, the first of whom died of cerebral injury the second from asphyxia following a gunshot wound of the neck with bleeding into the anterior mediastinum and compression of the trachea, and the third from a gas bacillus infection following a gunshot wound of the abdomen

Petechial hemorrhages were found most frequently in the pulmonary alveoli They occurred almost constantly in death from cerebral trauma but were also seen in the lungs of patients suffering from burns or from closed or open hemorrhage and dying a late death A peculiar form of petechial hemorrhage was noted in the spleens of patients dying from cerebral injury or from a slow open or closed hemorrhage into some other region of the body Such petechial hemorrhages presented themselves in the malpighian lymphatic nodules of the spleen and appeared to surround the central arteriole In many instances the entire lymphoid tissue of the nodule was replaced by a pool of blood Petechial hemorrhages were seen, in addition, in the renal pelves the ureters, the gastrointestinal mucosae and the adrenal glands in another 5 patients in this series The cause of death was cerebral trauma in 1 case, burns in 2 cases, a gunshot wound of the abdomen with hemoperitoneum in 1 case and a gunshot wound of the liver and biliary peritonitis in 1 case

It is evident that the occurrence of these petechial hemorrhages, especially in cases of simple compression of the brain by an extradural blood clot, cannot be explained adequately by those hypotheses which support the presence of a circulating toxin in secondary shock Hemodynamic alterations in the form of rapid and violent changes in blood pressure would appear to offer a more inclusive explanation In conclusion, it might be stated that it was possible to observe the frequent occurrence of macrophage cells containing an iron-pigment ("heart failure" cells) in the pulmonary alveoli of patients dying from shock associated with cerebral and other forms of trauma This is not in agreement with the findings of Moon and Kennedy,<sup>1</sup> who have stated that such cells are not found in the lungs of patients dying from shock

#### SUMMARY AND CONCLUSIONS

A study has been presented of visceral changes occurring in shock resulting from injuries to the head, the thorax, the abdomen and the extremities, from burns and from surgical operations The study is based on an analysis of 50 cases, in all of which postmortem examination was performed within one to three hours after death

The visceral changes are influenced by a variety of factors, which are enumerated and discussed

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<sup>14</sup> Kulbs, F, and Strauss, H Ueber subendokardiale Blutungen, *Klin Wchnschr* **12** 933 (June) 1933

The study of the syndrome of shock will be aided by investigations of the pathologic changes which occur in the tissues

A tentative pathologic grouping of the cases is set forth, not based on or biased by any specific theory of shock, but dependent solely on the pathologic changes observed at the autopsy table or under the microscope

It is suggested that such a grouping of cases is likely to aid in a more searching analysis of the syndrome of shock

The significance of anoxemia of the central nervous system in all forms of shock is emphasized in relation to the production of the pathologic changes

## ILLUSTRATIVE CASE REPORTS

### CEREBRAL TRAUMA

CASE 1—E S, a white man aged 31 was admitted to the John Gaston Hospital in Memphis in an unconscious state. He was thought to have been "slugged over the head." The temperature was 103 F, the pulse rate 60 per minute, the respiratory rate 40 and the blood pressure 110 systolic and 70 diastolic. The essential physical findings were a bruised area over the right eye, unequal dilatation of the pupils and rigidity of the left leg. Death occurred twenty minutes after admission, before any treatment could be instituted.

*Autopsy*—No fluid was present in the pleural or peritoneal cavities. The heart weighed 350 Gm. The right lung weighed 700 Gm. and the left 400 Gm. Both were firm and dark purplish. Thin bright red fluid exuded from the cut surfaces, the bronchi were filled with a pink frothy fluid. The spleen weighed 370 Gm. It was slate blue and very soft. The splenic pulp was soft and hemorrhagic and scraped readily. The liver weighed 2240 Gm. It was smooth and reddish brown. The gastrointestinal tract revealed moderate congestion of the gastric mucosa. The right kidney weighed 190 Gm and the left 200 Gm. Both revealed vascular congestion of the cortex and medulla.

Examination of the head revealed a subcutaneous hematoma over the right parietal and frontal regions and a Y-shaped fracture of the skull, without depression. A large extradural clot (11.5 by 8.5 by 4 cm.) compressed the right frontal and parietal lobes of the brain. There was no gross destruction of the brain tissue.

Microscopic examination of the lungs revealed congestion of the alveolar capillaries and considerable fluid in the alveoli and bronchioles. Red blood cells were found in the alveoli and bronchioles and there was a moderate number of "heart failure" cells. The spleen was markedly congested. Red blood cells appeared to be undergoing hemolysis. There was much iron-containing pigment inside the macrophages and also lying free. There was moderate congestion of the blood vessels of the liver, and swelling and vacuolation of the liver cells. No iron-containing pigment was present.

CASE 2—J W, a Negro man aged 29 was admitted to the John Gaston Hospital in Memphis in an unconscious state with a gunshot wound of the head. The pulse rate was 120 per minute and the blood pressure 106 systolic and 60 diastolic. Death occurred within six hours.

*Autopsy*—No fluid was found in the pleural or peritoneal cavities. The heart weighed 340 Gm. The chambers were not dilated. The right lung weighed 720 Gm and was soft, elastic and air containing. The left lung weighed 640 Gm and

was congested at the base. The spleen weighed 160 Gm. It was firm and dark red. The liver weighed 1,580 Gm and presented no gross pathologic changes. There were no gross changes in the gastrointestinal tract. The right kidney weighed 180 Gm and the left 170 Gm.

Examination of the head revealed hemorrhage into the tissues of the scalp. The dura mater was torn at the sites of entrance and exit of the bullet and at these points large hematomas lay beneath the dura. There was marked destruction of the tissue of the left cerebral hemisphere.

Microscopic examination of the lungs revealed considerable emphysema. There was marked congestion of the alveolar capillaries, and fluid and red blood cells were found in the alveolar spaces. There was a moderate number of "heart failure" cells. The sinusoids and capillary spaces of the spleen were markedly congested, and many macrophage cells contained iron pigment. The capillaries of the liver were congested in the region of the central veins. The kidneys revealed marked vascular congestion and parenchymatous degeneration of the tubular epithelium. Examination of the brain revealed hemorrhage into the cerebral tissue, with necrosis and infiltration by polymorphonuclear leukocytes. Phagocytic mononuclear cells contained iron pigment. The remaining viscera showed congestion of the capillaries.

#### TRAUMA TO ABDOMEN AND THORAX

##### *Early Death with Open Hemorrhage*

CASE 3—J. C., a Negro man aged 59, was admitted to the John Gaston Hospital in Memphis with a gunshot wound of the upper part of the abdomen. The intravenous administration of fluids was without avail, and death occurred eight hours later.

*Autopsy*—The peritoneal cavity contained 1,800 cc of fluid and clotted blood. There was no fluid in the pleural cavities. The heart weighed 470 Gm and the left ventricle was hypertrophied. The right lung weighed 400 Gm and the left 360 Gm. Both presented mild congestion. The spleen weighed 80 Gm and was dry and contracted. The liver weighed 1,680 Gm and there was a large laceration, surrounded by hemorrhage, in the left lobe. Examination of the gastrointestinal tract gave essentially negative results. There was no evidence of vascular congestion, and the vessels were contracted and contained little blood. The right kidney weighed 160 Gm and was pale. The left weighed 210 Gm, and the upper pole was lacerated by the passage of the bullet.

Microscopic examination of the lungs revealed marked emphysema but no edema. There were many "heart failure" cells in the alveolar wall and alveolar spaces. Examination of the liver revealed hemorrhage into the tissue, with mild early inflammatory cell invasion. The adjacent liver cells were edematous. Examination of the kidney revealed considerable hemorrhage into the renal tissue, with an infiltration by polymorphonuclear leukocytes.

*Comment*—The case just described illustrates that trauma to an organ, especially by a bullet, causes an increase in its weight, which is partly due to an infiltration of blood into the tissues and partly to an imbibition of fluid from the capillaries by the injured or dying cells. In some instances the fluid shift into an injured viscus may represent a considerable loss from the general circulation. The increase in weight of an injured viscus must therefore be taken into consideration in estimating the total diminution of the effective blood volume.

*Early Death with Closed Hemorrhage*

CASE 4—L P, a Negro youth aged 17 was struck by an automobile two hours before admission to the John Gaston Hospital in Memphis. Examination revealed a compound fracture of the left tibia and fibula a laceration of the left inguinal region, dislocation of the right hip joint and comminuted fractures of the pelvis on the right side. The temperature was 100.6 F the pulse rate 145 per minute, the respiratory rate 68 and the blood pressure 130 systolic and 80 diastolic. The red cell count was 4,000,000. The intravenous administration of fluids was without avail, and death occurred within eight hours.

*Autopsy*—The injuries already listed were found on postmortem examination, and, in addition, a badly comminuted fracture of the pelvic arch on the left side. There was a small amount of blood (50 cc) in the pelvis and several large hematomas were present in the mesentery of the small intestine. In the lower portion of the pelvis was a massive retroperitoneal hemorrhage which extended into the fat around the urinary bladder. There was no fluid in the pleural cavities. The heart weighed 320 Gm and was contracted but revealed no other pathologic change. The right lung weighed 400 Gm and the left 320 Gm both revealed moderate congestion and edema. The spleen weighed 80 Gm and was contracted and pale. The liver weighed 1,020 Gm and was pale and bloodless. The gastrointestinal tract was pale and the blood vessels contracted. The left kidney weighed 160 Gm and the right 150 Gm both were pale.

On microscopic examination the lungs showed marked congestion of the alveolar capillaries. Fluid was present in the alveoli together with red blood cells and "heart failure" cells. Examination of the spleen revealed the sinusoids and blood vessels to be empty of blood. The liver cells were moderately swollen and granular, there was no congestion of the blood vessels. The brain revealed congestion of the meningeal vessels.

CASE 5—L M, a Negro man aged 24 suffered a stab wound of the abdomen thirty minutes before admission to the John Gaston Hospital in Memphis. The temperature was 96 F the pulse rate 120 per minute and the blood pressure 76 systolic and 50 diastolic. The red blood cell count was 3,200,000, the white blood cell count 8,200 and the hemoglobin 9.4 Gm per cent. The intravenous administration of fluids was without avail and death occurred at the end of ten and a half hours.

*Autopsy*—Large hematomas were found in the left psoas muscle. There was no fluid or blood in the peritoneal cavity or the pleural cavities but large hematomas were found in the mesentery of the small intestine and the transverse mesocolon. The heart weighed 300 Gm. It was contracted and the myocardium was pale. The right lung weighed 650 Gm and the left 480 Gm. The lung tissue on both sides was dark reddish purple and firmer than normal. A thin reddish fluid could be squeezed from the cut surfaces. The spleen weighed 90 Gm and was contracted and relatively bloodless. The liver weighed 1,480 Gm and the parenchyma was pale. The gastrointestinal tract was pale and presented no evidence of vascular congestion. The left kidney weighed 150 Gm and the right 140 Gm. The parenchyma was pale.

Microscopic examination of the lungs showed marked congestion of alveolar capillaries. Many alveolar spaces were filled with fluid, red blood cells and numerous macrophage cells containing iron pigment. Occasional areas of emphysema and atelectasis were observed. Examination of the spleen revealed that the sinusoids and capillaries contained little or no blood there were no evidences of iron blood pigment. There was cloudy swelling of the hepatic cells the central vessels were not congested. There was cloudy swelling of the epithelium of the convoluted tubules of the kidneys.

### *Early Death with Regional Segregation of Blood*

CASE 6—T M, a white man aged 23, suffered a stab wound of the left side of the chest at the fifth intercostal space in the midclavicular line. The injury occurred half an hour before he was admitted to the John Gaston Hospital in Memphis, and death took place before treatment could be instituted.

*Autopsy*—There was no fluid in the pleural or peritoneal cavities. The pericardial cavity contained 500 cc of freshly clotted blood. There was an incised wound of the right ventricle on the anterior surface. The left lung weighed 500 Gm and the right 650 Gm. Both were dark red and firm, and frothy fluid could be expressed from the cut surfaces. The spleen weighed 200 Gm. It was dark blue, firm and congested. The liver weighed 1,800 Gm and exhibited moderate vascular congestion. The gastrointestinal tract revealed congestion of the mesenteric vessels. The right kidney weighed 160 Gm and the left 180 Gm. The cortex and medulla were congested.

Microscopic examination of the lungs revealed marked congestion of the alveolar capillaries. The alveolar spaces were full of fluid, and there were many "heart failure" cells. Examination of the spleen revealed the blood vessels congested and much iron pigment present. The remaining viscera showed vascular congestion.

### *Early Death with Infection*

CASE 7—A M, a Negro man aged 53, suffered a gunshot wound of the left upper quadrant of the abdomen half an hour before admission to the John Gaston Hospital in Memphis. The temperature was 95 F, the pulse rate 120 per minute, the respiratory rate 24, and the blood pressure 60 systolic and 40 diastolic. The red blood cell count was 5,220,000 and the white blood cell count 27,450. The intravenous administration of fluids was without avail, and death occurred within twenty-eight hours.

*Autopsy*—The peritoneal cavity contained 500 cc of grape juice-colored fluid, and the left pleural cavity, 150 cc of straw-colored fluid. There was no fluid in the right pleural cavity. The pericardial cavity contained 15 cc of clear fluid. All the tissues of the posterior abdominal wall were discolored by extensive interstitial hemorrhage and were markedly swollen and soft in consistency. Anaerobic cultures from this area were made within an hour after death and revealed a growth of *Cl. welchii* and *Bacillus coli*. The tissues of the left renal fossa were hemorrhagic.

The heart weighed 340 Gm and was contracted. The right lung weighed 660 Gm and the left 510 Gm. Both were dark reddish purple and firmer than normal. Reddish, frothy fluid could be expressed from the cut surfaces. The spleen weighed 180 Gm and was firm in consistency. The surface was dark blue and the cut surfaces reddish brown. The stomach and small intestine were dilated with gas, but the remainder of the gastrointestinal tract revealed nothing of note. The pancreas showed a moderate amount of hemorrhage into the tissues surrounding the distal half. The right kidney weighed 170 Gm and the left 180 Gm. Both showed a moderate degree of vascular congestion.

Microscopic examination of the lungs showed fluid in the alveoli. Numerous "heart failure" cells containing iron pigment were observed, and the red blood cells in the alveoli were undergoing hemolysis. The spleen revealed extreme engorgement of the blood vessels with red blood cells, many of which were undergoing disintegration, much iron containing pigment was noted. The central capillaries of the liver were moderately engorged with blood. There was parenchymatous degeneration of the liver cells, and the Kupffer cells contained iron pigment. The intertubular capillaries of the kidneys, as well as the glomerular

capillaries, were congested. The remaining viscera showed a moderate grade of vascular congestion.

### *Delayed Death with Open Hemorrhage*

CASE 8—D W, a Negro man aged 22, was admitted to the John Gaston Hospital in Memphis shortly after he had sustained a bullet wound of the left side of the chest. Dyspnea was present, and rapidly increased. Nine hundred cubic centimeters of blood was removed from the left thoracic cavity two days after admission. The bleeding continued, and death occurred four days later.

*Autopsy*—The mucous membrane and skin were pallid. No fluid or blood was present in the peritoneal cavity. The left pleural cavity contained 1,500 cc of blood, which was partially coagulated. There was no fluid in the right cavity. The left lung was airless and collapsed, the right lung was voluminous, moist and congested. The heart weighed 300 Gm, it revealed no significant changes. The spleen weighed 340 Gm and was soft, the pulp scraped readily. The liver weighed 1,600 Gm and was pale. The left kidney weighed 220 Gm and the right 200 Gm. The remaining viscera showed no changes.

Microscopic examination of the lungs revealed congestion of the alveolar capillaries. The alveolar spaces were filled with fluid fibrin, polymorphonuclear leukocytes and large mononuclear cells which contained brown pigment. The spleen showed cellular hyperplasia. The kidneys revealed cloudy swelling of the tubular epithelium of the convoluted tubules.

## TRAUMA DUE TO BURNS

### *Early Death*

CASE 9—B Y., a Negro woman aged 26 was admitted to the John Gaston Hospital in Memphis with extensive burns of the body. The red blood cell count was 6,176,000 and the white blood cell count 38,000, the hemoglobin was 19 Gm per hundred cubic centimeters. Intravenous fluids were administered, but no improvement was observed, and death occurred five hours after admission to the hospital.

*Autopsy*—Extensive burns covered the body from head to foot. The upper portion of the body presented second degree burns and the lower portion, third and fourth degree burns. No free fluid was observed in the peritoneal or pleural cavities. The pericardial sac contained 10 cc of clear straw-colored fluid. The heart weighed 340 Gm and was contracted. The right lung weighed 385 Gm and the left 350 Gm. Both were congested and edematous and frothy fluid exuded from the cut surfaces. The spleen weighed 120 Gm and was moderately firm. The cut surface was dark and reddish purple. The liver weighed 1,160 Gm and was of normal consistency. The color was pale yellowish brown. The gastrointestinal tract presented no changes. The right kidney weighed 110 Gm and the left 140 Gm. Both were dark purple. On the right side were numerous petechial hemorrhages into the mucosa of the pelvis and the upper end of the ureter. The remaining viscera presented no gross pathologic changes.

Microscopic examination revealed that the alveolar capillaries of the lungs were extremely congested. The alveoli contained considerable fluid, in which were red blood cells and desquamated alveolar epithelium. Occasional heart failure cells containing iron pigment were observed. The sinusoids and capillaries of the spleen were markedly congested and increased amounts of iron pigment were present. The liver revealed mild fatty metamorphosis. The tubular epithelium of the kidneys had undergone marked parenchymatous degeneration and many of the tubules and glomeruli contained brownish pigment. The capillaries of the adrenal glands were congested and the medullary tissue was edematous.

*Delayed Death*

CASE 10—F L, a Negro woman aged 19, suffered first and second degree burns of the left arm, the right axilla, the back and the abdomen just before she was admitted to Charity Hospital of Louisiana at New Orleans. Fluids were administered intravenously to the limit of safety, but were without effect, and death occurred five days after the injury.

*Autopsy*—The subcutaneous tissues of the entire body were found to be markedly edematous. There was no fluid in the peritoneal cavity. Each of the pleural cavities contained approximately 300 cc of clear straw-colored fluid, and the pericardial cavity contained approximately 100 cc of the same type of fluid. The heart weighed 250 Gm and revealed no gross pathologic changes. The right lung weighed 750 Gm and the left 600 Gm. Both were firm and reddish purple. Considerable frothy fluid escaped from the cut surfaces. The spleen weighed 220 Gm. It was firm and purplish brown. The liver weighed 1,600 Gm. It was yellowish brown and firm. The mucosa of the stomach and jejunum appeared diffusely hemorrhagic, with marked vascular congestion and numerous petechial hemorrhages. No evidences of ulceration were observed at any point along the gastrointestinal tract. The left kidney weighed 180 Gm and the right 170 Gm. Both were firm and reddish brown. The right adrenal gland revealed no gross pathologic change, on the left side gross hemorrhage had occurred into the medulla and cortex of the gland.

Microscopic examination of the lung revealed marked congestion of the alveolar capillaries. Fluid, red blood cells and "heart failure" cells were observed in the alveolar spaces. In the spleen the sinusoids were packed with red blood cells undergoing disintegration. Large amounts of iron-containing pigments were present both within the macrophage cells and free in the tissues. Fatty metamorphosis was observed in the liver. The stomach wall revealed extreme congestion of the mucosal and submucosal capillaries, with free hemorrhage into the tissues. There was no necrosis of the epithelium. The glomerular capillaries of the kidney were markedly congested, and the tubular epithelium exhibited parenchymatous degeneration.

## TRAUMA DUE TO OPERATION

CASE 11—S M B, a Negro woman aged 36, was operated on at Charity Hospital of Louisiana at New Orleans for uterine fibroids. Subtotal hysterectomy was done, with the patient under ether anesthesia. Four hours after the operation she went into a state of shock from which she never emerged. There was no response to intravenous fluid therapy or to blood transfusion. Death occurred thirty-six hours after operation.

*Autopsy*—The peritoneal cavity contained 1,000 cc of blood. There was no fluid in the pleural cavities. The pericardial cavity contained 40 cc of straw-colored fluid. The heart weighed 300 Gm and was contracted. The right lung weighed 320 Gm and the left 230 Gm. Both contained air and were pinkish gray. The spleen weighed 220 Gm. It was firm, dark blue and congested. The liver weighed 1,900 Gm. It was firm and reddish brown. The only pathologic change observed in the gastrointestinal tract was a moderate congestion of the mesenteric and omental blood vessels. The right kidney weighed 240 Gm and the left 260 Gm. The blood vessels of the renal cortex and medulla were congested.

Microscopic examination revealed the alveolar capillaries of the lung to be markedly congested. Numerous "heart failure" cells were present in the alveolar spaces. No edema was observed. The sinusoids and capillaries of the spleen were markedly engorged with red blood cells. The capillaries in the neighborhood of the central veins of the liver were congested. The other viscera showed evidences of vascular congestion.

# DIFFERENTIAL DIAGNOSIS OF MECHANICAL AND PARALYTIC ILEUS

WITH SPECIAL REFERENCE TO EARLY DIAGNOSIS OF  
STRANGULATED OBSTRUCTION

I B HAWORTH M D

AND

L H GARLAND M D

SAN FRANCISCO

A series of abdominal roentgenograms recently encountered at the San Francisco Hospital led us to review the subject of the differential diagnosis of intestinal obstruction from the roentgenologic standpoint and to make a tabular study

From approximately 250 cases in which either a clinical or a roentgen diagnosis of intestinal obstruction was made 100 cases were selected in which satisfactory roentgenograms were available and in which the diagnoses were established by observation made at operation or at post-mortem examination or by what we considered incontrovertible clinical evidence. The distribution of these 100 cases according to final diagnosis is given in table 1

The criteria by which the roentgenologic diagnosis of acute intestinal obstruction may be made have been outlined by Laurell<sup>1</sup> Wangensteen,<sup>2</sup> Granger,<sup>3</sup> Eliason and Johnson<sup>4</sup> and many others. The differential diagnosis between distention from mechanical obstruction and distention from peritonitis (paralytic ileus) or from another cause has also been discussed.<sup>5</sup> We endeavored to select the more important of these criteria and tabulated our cases according to the relative frequency

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From the Department of Medicine (Division of Radiology) of the Stanford University School of Medicine and the Department of Public Health of the City of San Francisco (J C Geiger Director)

1 Laurell, H. Roentgenologic Signs of Abdominal Effusions. Roentgen Diagnosis of Peritonitis, *Acta radiol* **5** 63-104 1926

2 (a) Wangensteen, O H and Paine J R. Treatment of Acute Intestinal Obstruction by Suction with the Duodenal Tube. *J A M A* **101** 1532 (Nov 11) 1933. (b) Wangensteen O H. Rationalizing Treatment in Acute Intestinal Obstructions, *Surg, Gynec & Obst.* **64** 273 (Feb 15) 1937

3 Ochsner, A, and Granger, A. Roentgen Diagnosis of Ileus. *Ann Surg* **92** 947-958 (Dec, pt 1) 1930

4 Eliason E L, and Johnson J. Diagnostic Features of Ileus. *Radiology* **26** 342-348 (March) 1936

5 (a) Laurell<sup>1</sup> (b) Ochsner and Granger<sup>3</sup>



and severity of these findings in each of several common pathologic conditions. Each roentgenogram was scrutinized carefully, and the data given under the headings of table 2 were recorded.

By the separation of the cases into the clinicopathologic groups listed in table 2, a relatively high correlation of the data for each group was obtained. The presence of this high correlation leads us to believe that there exists a more or less characteristic pattern of findings in cases of

TABLE 1—*Final Diagnoses in One Hundred Cases of Intestinal Obstruction or Paralytic Ileus*

Final Diagnosis	Roentgen Diagnosis (Proved)	
	I Obstruction Group	
	Small Bowel Obstruction	Large Bowel Obstruction
Adhesions	27	1
Volvulus	2	4
Hernia	12	
Carcinoma of colon		8
Fecal impaction		5
Mesenteric thrombosis	1	1
Regional ileitis	1	
Intussusception	1	
Gallstone impaction	1	
Carcinoma of cervix with extension	1	
	II Ileus Group	
	Ileus with Peritonitis	Ileus without Peritonitis
Pelvic inflammatory disease	6	1
Perforated viscus	5	
Appendicitis	7	
Postoperative peritonitis	2	
Cholecystitis		3
Acute enteritis		2
Diverticulitis	2	
Peritonitis	2	
Typhoid fever		1
Morphine addiction		1
Pyelitis		1
Functional vomiting		1

intestinal obstruction or paralytic ileus, which, considered with the clinical history, should enable the radiologist to arrive at an accurate diagnosis in most instances. The roentgenologic findings alone, however, are inadequate for diagnosis in about 15 per cent of cases, this is shown by the selected cases presented in table 3, which are illustrative of the possibilities of error when the clinical findings are not given due consideration.

An abnormal amount of gas was found distributed in various portions of the intestinal tract in all of our cases except the 2 instances of

TABLE 2—*Differential Diagnostic Findings (Graded + to ++++ According to Severity) in Eighty-Seven Typical Cases of Intestinal Obstruction and Paralytic Ileus\**

Diagnosis	Number of Cases	Average Duration of Symptoms in Hours	Average Amount of Gas in Intestinal Tract	Degree of Distention of Small Bowel	Fluid Levels	'Thickening' of Bowel Wall	Visibility of Properitoneal Fat Line	Degree of Distention of Large Bowel
Early small bowel obstruction † simple	7	15	++	++	+++	±	+++	±
Early small bowel obstruction † strangulated‡	8	18	++	++	++	++	++	±
Late small bowel obstruction † simple	20	65	+++	+++	+++	++	+++	±
Late small bowel obstruction † strangulated	6	48	+++	+++	+++	+++	+	+
Appendicitis perforated	7	56	+++	++	++	++	+	++
Peritonitis due to pelvic inflammatory disease	6	96	++	±	+	++	++	++
Peritonitis due to other causes	12	80	+++	++	++	++	++	++
Acute cholecystitis	3	32	++	+	+	+	++	++
Large bowel obstruction	9	112	+++	±	++	++	++	++++
Large bowel volvulus	4	114	++++	±	+++	++++	+	+++
Fecal impaction	5	(20-48) 33	++	++	+	±	+++	++

\* Data on the other 13 cases are listed in table 3

† Early obstruction is that observed within twenty four hours of the onset of the symptoms; late obstruction after that time

‡ Strangulated obstruction is obstruction associated with partial or complete occlusion of the vascular supply of the involved segment of bowel; peritoneal exudate appears early in such cases and prompt surgical intervention is imperative

TABLE 3—*Differential Diagnostic Findings in Thirteen Atypical Cases of Intestinal Obstruction and Paralytic Ileus\**

Diagnosis	Number of Cases	Average Duration of Symptoms in Hours	Average Amount of Gas in Intestinal Tract	Degree of Distention of Small Bowel	Fluid Levels	Thickening of Bowel Wall	Visibility of Properitoneal Fat Line	Degree of Distention of Large Bowel
Acute enteritis	2	95	+++	+++	++	+++	+	+
Typhoid fever	1	102	+++	++	+++	±	+++	+
Acute obstruction † strangulated	2	30	0	0	0	0	++	0
Morphine addiction	1	96	+++	+	0	++	+++	++
Mesenteric thrombosis colon	1	240	++++	0	?	++	+++	++++
Mesenteric thrombosis, ileum	1	72	++	++	+++	+	+++	+
Regional ileitis	1	1 yr	++	+	?	++	+	++
Pyelitis	1	60	++	0	0	+	0	+
Chronic pelvic inflammatory disease	1	45	++	0	?	+	++	+
Gallstone impaction † duodenum‡	1	120	++++	0	?	+++	+	+++
Functional vomiting	1	48	++	0	?	+	+++	++

\* The method of grading is the same as that followed in table 2.

† A question mark indicates that no upright or lateral decubitus roentgenogram was available to indicate the presence or absence of fluid levels

‡ This condition was complicated by peritonitis and secondary ileus (note the duration five days)

acute obstruction listed in table 3. We are unable to explain the absence of gaseous distention in these 2 cases. We did not find that the amount of gas in the stomach, if it was present at all, was of any significance.

Gaseous distention of the small intestine occurs in many different conditions. The mere presence of gas shadows in roentgenograms of the small bowel, unattended by significant distention of the lumen, is of little importance. It is well known that swallowed air passes readily into the small bowel when the person is in the recumbent or in the left lateral decubitus position.<sup>6</sup> However, when distention is present accompanied by abdominal pain, nausea, vomiting and obstipation



Fig. 1—Roentgenograms taken in 2 cases of early obstruction of the small bowel, illustrating the difference in the apparent thickness of the bowel wall in cases of simple obstruction as compared with those of strangulated obstruction. *A* shows several dilated, gas-filled loops of jejunum with normal "wall thickness." The patient was a 42 year old woman, who had cramps and nausea for eighteen hours and vomiting for four hours. Operation showed ileal obstruction due to adhesions, there was no peritonitis. *B* shows several dilated, gas-filled loops of jejunum with abnormal "wall thickness" (i. e., peritoneal fluid). The patient was a man aged 53 years, who had pain, nausea and vomiting for twelve hours. Operation showed ileal obstruction due to an incarcerated left inguinal hernia, there were peritoneal exudate and infection.

mechanical or paralytic ileus is fairly certain to be present. If the symptoms are of less than forty-eight hours' duration, if fluid levels are present, if the bowel wall is not "thickened" (separated) by peritoneal

6 Van der Burg, L. W. Over het elimineeren van darmgassen, storend voor de röntgendiagnostiek, Thesis Bandoeng Java, 1937.

exudate and if the properitoneal fat line<sup>7</sup> is evident, then acute mechanical obstruction should be suspected.

If apparent thickening of the bowel wall is seen (peritoneal exudate), with or without partial obscuration of the properitoneal fat line, the probable cause is either a strangulated intestinal obstruction or peritonitis with paralytic ileus. Significant distention of the large intestine is evidence of paralytic ileus. In cases in which the condition is of more than forty-eight hours' duration these differential characteristics are lost, according to our experience, this is presumably due to peritoneal irritation and "secondary" ileus following long-standing obstruction from any cause.

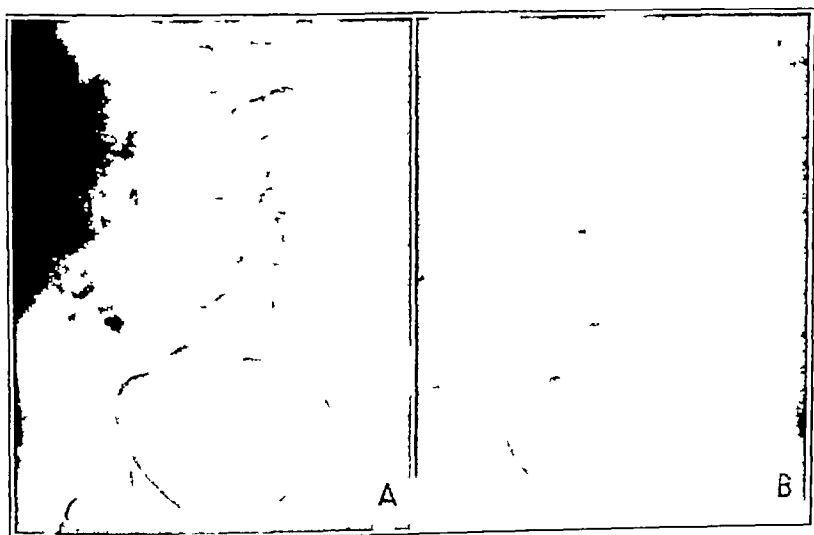


Fig. 2—Roentgenograms taken in 2 cases of late obstruction of the small bowel, illustrating greater distention of the bowel as compared with the cases of earlier stages illustrated in figure 1. These cases also show the difference between nonstrangulated and strangulated obstruction. *A* shows several gas-dilated loops of small bowel with a small amount of peritoneal exudate. The patient, a woman aged 62 years, had cramps and vomiting for thirty-four hours. Operation showed ileal obstruction due to adhesions, there was no peritoneal infection. *B* shows several gas-dilated loops of jejunum separated by a large amount of peritoneal exudate. The patient, a man aged 46 years, had cramps, nausea and vomiting for two days, an enema elicited bloody stools. Operation showed ileocolic intussusception due to an ileal polyp, peritonitis was present.

We have learned to place much greater confidence in the presence of peritoneal exudate, as shown by apparent thickening of the bowel wall.

7 The properitoneal fat line is the line of diminished density observed in the lateral portions of abdominal roentgenograms mesial to the soft tissues of the abdominal wall, it lies in the area between the iliac crests and the lower ribs. Its obliteration is suggestive of peritonitis and is presumably due to edema of the fatty tissues (cf. the obliteration of the psoas margin in perinephric inflammation).

(that is, separation of adjacent loops of bowel), than in the obliteration of the properitoneal fat line as an indication of the presence of peritoneal irritation, or peritonitis. The fat line was present in some of our cases of peritonitis of long standing, and was absent in a fair number of our cases in which no peritoneal exudate could be demonstrated. Occasionally, when two roentgenograms were made of the same patient at one examination, one of the roentgenograms showed the line clearly and the other showed no such shadow. When considered with other roentgenologic findings, however, the properitoneal fat line is often of definite assistance in diagnosis.

Gas was present in the colon in the majority of cases in this series whether the distention was due to mechanical obstruction or to paralytic

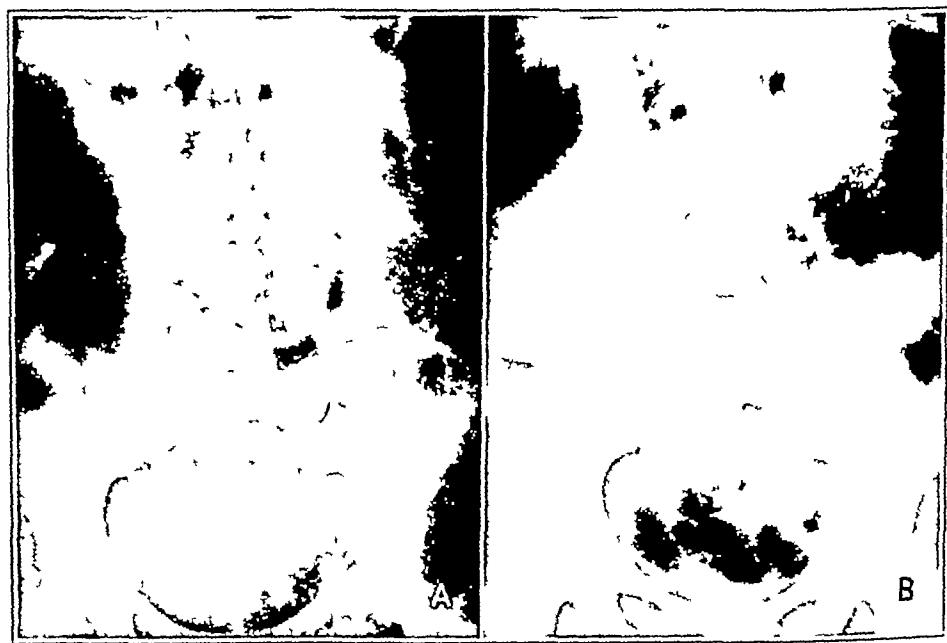


Fig 3—Roentgenograms taken in 2 cases of paralytic ileus, illustrating marked gaseous distention and moderate peritoneal exudate. *A* shows gas-dilated loops of small and large bowel and peritoneal exudate. The patient was a woman aged 30 years, who had nausea, vomiting, abdominal pain and diarrhea for three days. The clinical diagnosis was ruptured appendix with peritonitis. Conservative treatment was given and was followed by recovery. *B* shows gas-dilated loops of small and large bowel with some peritoneal exudate. The patient was a diabetic woman, aged 62 years, who had nausea, vomiting and abdominal pain for five days as well as some diarrhea. The clinical diagnosis was acute enteritis and diabetic acidosis. Conservative treatment was followed by recovery. Examination of the stools did not reveal *Bacillus dysenteriae*, *Bacillus typhosus* or *Bacillus paratyphosus A* or *B*.

ileus. Any considerable distention of the colon led us to suspect peritonitis or some other cause of paralytic ileus unless the condition was in a late stage (duration over forty-eight hours). The absence of fluid levels in roentgenograms made with a horizontal beam was, in our

experience, good evidence of the absence of true obstruction or paralysis of the bowel, for example, "dry" collections of gas are common accompaniments of such condition as pyleitis and ureteral colic. We tried to obtain roentgenograms with the patient in an upright position when his condition warranted, in other cases posteroanterior roentgenograms made with the patient in the left lateral decubitus position were satisfactory.

#### SUMMARY AND CONCLUSIONS

Roentgenographic findings in 100 proved cases of mechanical or paralytic ileus are presented in tabular form.

Early stages of acute mechanical intestinal obstruction due to adhesions or bands can often be differentiated roentgenologically from strangulated obstruction and from peritonitis.

Late stages of mechanical obstruction are frequently difficult to distinguish roentgenologically from paralytic ileus and from mesenteric thrombosis.

Consideration of the clinical history and findings is essential for the intelligent interpretation of abdominal roentgenograms in cases of suspected intestinal obstruction.

There is a small group of cases in which no roentgen evidence of intestinal obstruction is found, even though complete obstruction is present. For this reason a negative roentgenologic report must not preclude careful clinical observation of the patient, supplemented by repeated roentgenographic examinations at short intervals (about four hours), until a diagnosis is established.

# REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, M D  
LOS ANGELES

FRANK HINMAN, M D  
SAN FRANCISCO

ALEXANDER von LICHTENBERG, M D  
BUDAPEST, HUNGARY

ALEXANDER B HEPLER, M D  
SEATTLE

ROBERT GUTIERREZ, M D  
NEW YORK

GERSHOM J THOMPSON, M D  
AND

JAMES T PRIESTLEY M D  
ROCHESTER, MINN

EGON WILDBOLZ, M D  
BERNE, SWITZERLAND  
AND

VINCENT J O'CONOR, M D  
CHICAGO

## KIDNEY

*Surgical Technic*—Bonanome<sup>1</sup> stated that, although resection of the kidney is not a new type of intervention, it has within recent years received more attention as the result of improvements in its technic. Furthermore, the improvements that have been achieved in diagnosis have made it possible to recognize the precise indications for this operation.

Partial nephrectomy may be subdivided into two types—polar (renal amputation) and median (renal resection). Bonanome gave the name of renal resection to the latter only. On the basis of an illustrative case, he concluded that this operation is attended by no more dangers than is common nephrectomy and that it should be carried out whenever the proper indications are present. If the portion of kidney to be removed contains a cavity, as it did in the case cited, it is advisable first to open this cavity in order to learn the points at which the incisions should be made in the kidney for the resection.

During resection of the renal parenchyma the author has never observed such hemorrhages as might necessitate making compression

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<sup>1</sup> Bonanome, L. Contributo alla resezione renale. Caso clinico, *Urologia* 6 3-6 (March) 1939

on the renal pedicle, but the surgeon should always bear in mind the possibility of such an occurrence. Small bleedings have always been controlled easily by use of hot compresses and by approximation of the sectioned flaps. In no case has it been necessary to have recourse to interposition of autoplasmic or heteroplasmic substances for hemostasis, nor has there been any secondary hemorrhage.

In Bonanome's opinion the surgeon should discard, whenever possible, the method of interposition of fatty or muscular tissues as a covering, for hemostasis it is unimportant and for reconstruction it is nearly always enough to approximate the sectioned flaps if the surgeon bears this in mind during section.

It is desirable to bring the margins together by means of double catgut sutures that bite far into the capsule and parenchyma, as in the case cited. In this way it is possible to make much greater traction on the sutures in drawing the flaps together without their cutting the substance of the parenchyma. Furthermore fewer sutures are required to reconstruct the kidney. The capsule is then sutured separately in addition. No fistula has ever resulted after performance of this operation by the author and his associates.

Mathe<sup>1a</sup> stated that clampless nephrectomy is the operation of choice in dealing with kidneys in which such conditions as ectopia, incomplete rotation and aberrant distribution of blood vessels are present, in dealing with horseshoe kidney and in those cases in which the surgeon is called on to remove a kidney destroyed by tuberculosis, pyohydronephrosis, formation of abscess or calculous disease. It is also indicated for removal of the hydronephrotic kidney, in which the elongated vessels readily lend themselves to clampless ligation.

Clampless nephrectomy is contraindicated for patients suffering from extensive perirenal fibrosis, for patients with kidneys with a short pedicle, for patients presenting extensive scar formation resulting from previous operations and in cases of renal tumor.

Mathe's technic calls for adequate exposure, careful dissection and meticulous manipulation of the renal blood vessels. Clampless nephrectomy is simplified and made safer by dissecting the pedicle free with a mounted cherry sponge and by utilizing a nontraumatizing curved mosquito forceps in order to place the ligature around the blood vessels that are to be ligated.

Clampless nephrectomy was successfully performed on 20 patients. Success depends on careful, clean-cut dissection which prevents injury to surrounding structures. It assures a more nearly perfect specimen is accompanied by less shock and is followed by a smoother convalescence than is the case with other procedures.

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<sup>1a</sup> Mathe, C. P. Clampless Nephrectomy. *J. Urol.* **42**: 1135-1144 (Dec.) 1939.



Hess<sup>2</sup> discussed resection of the rib in renal operations, a procedure which he said he has been carrying out for twelve years. An incision is made in the skin over the twelfth rib, the rib is dissected free and is then resected from its attachment at the vertebra. The kidney, surrounded by Gerota's capsule, is then separated posteriorly as far as the pedicle. This is done with the surgeon's fingers, by finding the line of cleavage between Gerota's capsule and the transversalis fascia. Gerota's capsule is then opened on the posterior surface of the kidney, near the hilus, and the incision is enlarged with the fingers.

The advantages of the incision are (1) simplicity of operative exposure of the whole kidney and adrenal region with a relatively small incision, (2) protection of the iliohypogastric, ilioinguinal and intercostal nerves and vessels, preventing anesthesia of the lower abdominal quadrant, (3) less direct trauma to the muscles of the abdomen (which are always severely injured by all other incisions in the loin), preventing postoperative hernia, and (4) the fact that retraction is seldom necessary and, when it is, need not be very forceful.

*Hydronephrosis*—Berkman and Priestley<sup>3</sup> described a symptom complex occasionally produced by unilateral uninfected hydronephrosis, which is characterized by a dull, aching, nonextending pain in the upper part of the abdomen. This pain is usually aggravated by activity of the patient in the erect posture and relieved by his reclining on the back, on the opposite side or, rarely, on the affected side. It is frequently accompanied by anorexia and nausea, sometimes severe, and occasionally by vomiting. Berkman and Priestley emphasized the importance of recognizing this symptom complex. Patients who present these complaints without apparent organic disease to explain their symptoms frequently may be considered neurotic, because physical examination, urinalysis and roentgen studies of the gastrointestinal tract, kidneys, ureters and bladder may reveal nothing abnormal. Intravenous urographic examination is the best method of confirming the suspicions which the patient's history may arouse. Treatment is surgical. The best type of surgical procedure to employ depends on the cause and nature of the hydronephrosis. Sixteen instances of the condition have been encountered, 4 of which are presented in detail.

*Tumors*—Ostrum and Fetter<sup>4</sup> stated that advanced renal malignant disease frequently exists without symptoms referable to the organ of

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2 Hess, E. Resection of the Rib in Renal Operations, *J Urol* **42** 943-949 (Dec) 1939.

3 Berkman, J. M., and Priestley, J. T. The "Position-Relief Syndrome" of Hydronephrosis, *Minnesota Med* **22** 217-222 (April) 1939.

4 Ostrum, H. W., and Fetter, J. S. Silent Nephroma, *J Urol* **43** 39-51 (Jan) 1940.

origin but, rather, with symptoms pointing almost exclusively to sites of distant metastases

The usual clinical triad of hematuria, pain and abdominal tumor is by no means essential to the focusing of clinical suspicion on the urinary tract. If any one of these three clinical manifestations is observed, "a urodiagnostic study is indicated, provided a definite diagnosis is not otherwise forthcoming in due time."

When a malignant bone lesion is noted or suspected in the course of radiographic or roentgenoscopic examination, particularly in the aged, the urologist always should investigate the kidneys before concluding that the condition has been sufficiently studied.

The occurrence of even a single episode of gross or microscopic hematuria should always be noted with serious concern.

Maslow<sup>5</sup> reported 3 cases of Wilms's tumor with the possible existence of a fourth, in children of the same family. All 4 children were normal, had been delivered at full term and apparently had been normal in every respect until they were taken ill. There were 2 boys and 2 girls, and their ages ranged from 13 months to 4 years. The left side was involved in 3 children, the right, in 1. Abdominal tumor was the presenting symptom in 3 cases, and the fourth child was brought to the hospital with symptoms of intestinal obstruction. Hematuria was present in 1 case. According to the mother, in 3 of the children the onset of abdominal enlargement was preceded by an acute condition: acute tonsillitis in the first, injury from a fall in the second and severe chickenpox in the third. One patient received no treatment at all, 1 was operated on with a diagnosis of ileus, and an inoperable Wilms tumor was found, 1 underwent nephrectomy and postoperative roentgen therapy, and 1 received preoperative roentgen therapy followed by nephrectomy and postoperative roentgen therapy.

Smyth<sup>6</sup> stated that not infrequently hypernephromas develop silently and that metastasis may be the first sign of the disease. He reported 2 cases. In both there was an absence of urinary symptoms, and in both the metastasis first drew attention to the disease. In 1 case a tumor which was not palpable infiltrated the kidney rapidly and caused widespread dissemination, whereas in the other case a slow, indolent type of growth gave rise to solitary metastasis.

Smyth discussed the two classifications of Foulds and Braasch: alveolar carcinoma, which is the more malignant type, and adenocarcinoma, which is the less malignant type. The clinical history of the

5 Maslow, L. A. Wilms Tumor. Report of Three Cases and a Possible Fourth One in the Same Family, *J Urol* **43** 75-81 (Jan) 1940

6 Smyth, M. J. Silent Hypernephromata. *Brit J Surg* **27** 266-274 (Oct) 1939

less malignant type is sometimes remarkably prolonged. In some patients the disease has existed from twenty to forty years. One patient had had a palpable tumor for thirty years, and in another a growth was known to have existed for sixteen years.

Metastases may cause confusion, and in the absence of a biopsy investigation of the kidneys should not be forgotten. Smyth stated that evidence of only one metastasis should encourage the surgeon to undertake the double operation, since it may mean complete eradication of the disease.

Adams and Hunt<sup>7</sup> stated that Wilms's tumor of the kidney is the most common abdominal tumor in children.

The usual finding in cases of Wilms's tumor is an abdominal mass, frequently accompanied with loss of appetite, dilated superficial veins, vomiting and abdominal distress. Hematuria is rare. Some aspects of Wilms's tumor can be simulated by neoplasms of the adrenal gland, other retroperitoneal neoplasms, tumors of the liver and unusual congenital anomalies.

A reasonably accurate diagnosis should always precede heavy preoperative irradiation therapy. Radiosensitiveness is of no value in the differential diagnosis of Wilms's tumor.

Medulloblastoma of the adrenal gland is more radiosensitive than Wilms's tumor, and in certain cases of unverified Wilms's tumor in which the patients were reported cured by irradiation the tumor probably was medulloblastoma.

Preoperative irradiation followed by nephrectomy when practicable is advocated as the treatment of choice for Wilms's tumor.

Excretory urographic study after intramuscular injection of diodrast (a solution of 17 to 35 per cent 3,5-diiodo-4-pyridone-*N*-acetic acid and diethanolamine) is a safe and helpful diagnostic procedure in case of the existence of small or blocked veins and in the handling of uncooperative patients.

*Tuberculosis*—Howard<sup>8</sup> discussed the management of the ureter in the presence of tuberculous lesions of the kidney. He wrote that he removes the kidney in the usual manner, freeing it of its pedicle, but that he does not cut the ureter. The kidney, still attached to the ureter, is pulled out from the lower angle of the wound. The wound is covered with an alcohol-soaked sponge, and the kidney is cut from the ureter,  $\frac{1}{2}$  inch (1.27 cm) of the ureter being left protruding. A catheter or a glass connecting tip is introduced into the lumen and tied. This facili-

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7 Adams, P. S., and Hunt, H. B. Differential Diagnosis of Wilms Tumor Assisted by Intramuscular Urography, *J Urol* **42** 689-708 (Nov.) 1939.

8 Howard, T. L. The Management of the Ureter in Tuberculous Lesions of the Kidney, *J Urol* **42** 1003-1009 (Dec.) 1939.

tates treatment of the ureter and bladder by instillations or irrigations with any antiseptic medium or solution

Henline,<sup>9</sup> in discussing Howard's paper, said that the question of proper treatment of the tuberculous infected ureter after nephrectomy is still unsettled. Formation of draining sinuses has occurred after nephrectomy for tuberculosis in 67.7 per cent of 97 cases recently studied.

Most urologists believe that these sinuses result from infection in the stump of the ureter. However, some believe that the perirenal fat is already infected when tuberculosis of the kidney is discovered or becomes infected from manipulation during nephrectomy and that the wound will break down and form a sinus regardless of the treatment of the cut end of the ureter.

Following Howard's suggestion, Henline, in performing seven nephrectomies in 7 cases of tuberculous kidney, clamped and tied the pedicle, permitting the kidney to remain attached to the ureter until the entire wound was sutured. The ureter with the kidney attached emerged at the anterior angle of the wound.

The wound remained closed in 4 of the 7 patients, except at the site of the ureteral transplant to the skin. Two of the four ureteral wounds healed in fifty-four and eighty-three days respectively, and at the time of Henline's discussion the other two were still draining, two hundred and ten and seventy-five days respectively after operation.

The renal wounds of the remaining 3 patients opened, those of 2 closing in one hundred and eighty-six and one hundred and eight days respectively and the third continuing to drain eighty-five days after operation. Four ureteral stumps remained viable and were removed in an average of nineteen days after operation, whereas three of the stumps became necrotic and sloughed in sixteen days. No catheter or glass connecting tip was placed in any of these ureters.

Mycobacterium tuberculosis was discovered in the urine of each of these patients. The vesical symptoms had completely disappeared in 4 patients at the time Henline spoke and were much improved in 2, and 1 patient showed little symptomatic change.

Henline stated that the results achieved in treating these few patients by merely transplanting the ureter in the lowest angle of the wound have not reduced the morbidity following this operation as much as he had hoped.

Stone—Priestley<sup>10</sup> discussed the treatment for unilateral and bilateral stag-horn renal calculi.

<sup>9</sup> Henline, R. B., in discussion on Howard, *s. p.* 1033.

<sup>10</sup> Priestley, J. T. Treatment for Unilateral and Bilateral Stag-Horn Renal Calculi, *J. Urol.* **42**: 933-942 (Dec.) 1939.

Large, branched renal calculi often do not produce severe pain or other symptoms which direct attention to the urinary tract. Despite this fact, stones of this type, whether unilateral or bilateral, cause progressive renal damage. When a unilateral stag-horn calculus is present, the chance of removing the stone and preserving a functioning kidney is gradually reduced the longer operation is postponed. When bilateral stag-horn stones are present, the outcome under medical management is almost invariably progressive renal damage until renal insufficiency ensues. Stag-horn stones can be removed from the kidney when renal function is adequate, with a low operative risk and with the expectation of favorable late results in the majority of cases. Early operation for unilateral or bilateral branched renal stones usually seems advisable.

If renal function is diminished, a period of appropriate preoperative preparation is essential. The details of surgical management will vary somewhat in each individual case. Pelviolithotomy, if feasible, is the operation of choice, if not, nephrolithotomy is required. The insertion of a nephrostomy tube at the time of operation is desirable. Any obstructive factor at the ureteropelvic juncture should be relieved if the condition of the kidney and of the patient warrants such a procedure.

Gonzalez<sup>11</sup> observed that it is common for patients who have undergone conservative operation for septic stones of the kidney or of the ureter to manifest no improvement in their functional condition between entering and leaving the hospital. This led him to watch the mechanical and functional results for a longer period. Patients returned for troubles which could not be attributed to a return of lithiasis but were referable to lesions caused by the stone from the time of onset of the disease.

Seven patients were studied for an entire year after leaving the hospital. The time that these patients had suffered from symptoms of lithiasis before their operations ranged from two to twenty-six years. Anatomic and functional changes had occurred in every case, but they were worst in those patients who had suffered longest before coming to operation. The anatomic changes consisted chiefly of dilatation, especially when ureteral stones had been present. In such cases the lesions were even more pronounced and persistent, without modification, after operative treatment. In all there was infection. In every case there was deficiency of renal function. Examination showed that the function remains stationary or even becomes worse after conservative treatment (pyelotomy, ureterostomy). Surgical treatment, then, has not arrested the progressive course of functional changes. It is, therefore, evident that complete restoration must be considered improbable.

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11 Gonzalez, R. Étude de la fonction renale apres les operations conservatrices de la lithiase reno-ureterale, *J. d'urologie* 47 110-127 (Feb.) 1939

The importance of these changes depends on three factors (1) the stone and its localization, (2) the time elapsed and (3) presence of infectious processes. What has happened is that in replacing the damaged tissue, connective tissue has not only taken the place of normal tissue but has invaded the latter over a greater or lesser tract, according to the age of the lesions. This applies to changes in the ureter, pelvis and calices and explains why urologists cannot expect anatomic forms and histologic structures to regenerate. After these anatomic changes, the modifications of renal function depend on innumerable factors, the behavior of which is too complex to be determined. Gonzalez concluded in agreement with Hinman that the changes following complete obstruction of the ureters are alike in all species proportional to the degree of the lesion and that compensatory hypertrophy of the opposite kidney is progressive and becomes anatomically complete between the thirtieth and the fortieth day, although the functional reserve has not yet attained its maximal power.

He thus deduced that an obstacle causing changes in the renal parenchyma causes proportional hypertrophy in the opposite kidney. Animal experiments show that the renal parenchyma that is least injured is most likely to receive physiologic stimulants which control function and reparation. They show that repair of lesions is in inverse proportion to the time the lesions have been evolving. In cases in which the opposite kidney remains sound, this kidney alone is capable of meeting the needs of the situation. This explains why lesions of the diseased kidney remain stationary.

In clinical treatment, however, difficulties are met in appreciating the exact form of the renal activity, and the general ignorance of the intimate mechanism of renal function becomes apparent. It is evident that more study is necessary for an understanding of the upper part of the urinary apparatus in cases of renal stone, and also of the ureter, to determine the degree of the changes present. Prognosis must be reserved even after examination of the lesions. Treatment will depend on the ability of the urologist to arrive at a correct diagnosis with reference to the nature and extent of these lesions.

Birdsall<sup>12</sup> discussed the incidence of obstruction of the urinary tract in the formation of renal calculus. The subject matter of the paper comprises a study of 150 cases of renal calculi and 61 cases of ureteral calculi, totaling 211 cases of lithiasis of the upper portion of the urinary tract.

Nephroptosis with angulation of the ureter was the most frequently encountered type of obstruction of the urinary tract in association with

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<sup>12</sup> Birdsall, J. C. The Incidence of Urinary Tract Obstruction in Renal Calculus Formation, *J. Urol.* **42** 917-932 (Dec.) 1939.

which renal and ureteral calculi were found. In many cases comparatively small calculi were demonstrated by pyelographic studies to be situated in the minor calices, giving evidence of having been formed on the renal papillae. Many other types of obstruction, such as bands, vessels, stricture of the ureter and various types of anomalies, such as renal duplication, crossed ectopia, horseshoe kidneys and polycystic disease, were the underlying cause of hydronephrosis, stasis of urine and formation of calculus.

As a result of pyelographic studies, hydronephrosis was found to be present in 179, pyonephrosis in 23 and pyelonephritis in 9 cases. Infection also played an important role and was found in 168 cases, in 43 of which ureteral calculus was present and in 125 of which renal calculus was present.

Surraco<sup>13</sup> described a technic for extraction of large calculi from the kidney, in which he makes use of extrinsic pyelotomy instead of nephrotomy. His method takes advantage of the anatomic relations of the renal sinus, the pelvic cavities and the retropyelic vessels, all of which he discussed. The aim of his method is "to expose widely the posterior surface of the intrasinus pelvis and that of the primary calices" for the purpose of intrarenal exploration. The operation consists of five stages, illustrated in Surraco's paper by appropriate drawings. It begins like any decapsulation procedure, a flap of capsule being cut in the form of an arc. This curved flap then corresponds to a sector of the posterior wall near the renal sinus. It is easy to free the capsule into the renal sinus, separating it from the posterior wall of this sinus. It is likewise easy to separate the retropyelic vessels at the same time with the capsule, to which they remain adherent, thus leaving the posterior surface of the cavities of the pelvicalicular system completely free. The flap of capsule is then cut at its end, section being continued as far as the margin of the renal sinus. Then in front of the retropyelic veins, which have been brought down by a series of strokes, the flap is cut as far as the interior of the renal sinus, whereupon the pelvis becomes fully exposed, its posterior surface as well as that of the primary calices being in full view.

An incision along the axis of the pelvis will provide easy access to the calices. Then by digital exploration the mouth of each calix can be found, dilated and penetrated to its apex with bimanual palpation. The finger, introduced into the calices, discovers all irregularities and foreign bodies that may lie within them, extracts them and executes all necessary maneuvers.

By means of this procedure it is possible to extract all coralliform stones, no matter how complicated their formation may be, proceeding

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13 Surraco, L. A. L'extraction des gros calculs du rein, pyélotomie postérieure étendue pelvi-caliculaire, *J. d'urologie* 48 217-223 (Sept.) 1939.

separately in each calyx, and when there are small fragments, the exploring finger within the canaliculi can perform a miniature nephrotomy to help in the extraction

This method, therefore, permits the surgeon to explore with ease all the renal cavities, by double palpation, to discover every change which may exist within diverticular cavities, to remove stones of all sorts, even those with very complex arborizations, to make with the exploring finger complementary nephrotomies and to carry out ample drainage of all intrarenal cavities

*Rupture*—Peacock<sup>14</sup> reported a series of cases and stated that rupture of the kidney may be produced by apparently mild trauma. Diseased kidneys are more prone to rupture than healthy ones. Automobile accidents constitute the greatest causative agent. Hematuria, localized pain in the loin, tumefaction and shock are the commonest symptoms. Palpation and excretory urographic study are the best diagnostic aids. Expectant treatment is superior to immediate operation.

*Trauma*—Farman<sup>15</sup> stated that the incidence of traumatic rupture of the kidney is low but that such injuries appear to be on the increase, mainly because of modern traffic accidents. Farman reported 3 cases of total rupture of the kidney. In 2 the rupture was the result of an automobile accident, and in 1 it followed a football injury. Nephrectomy was performed in all 3 cases, with 1 death.

It is necessary to determine the extent and type of injury and the expected course. Aside from the history of trauma, the presence of hematuria, pain in the renal region and some degree of shock, the physical observations are important in determining the severity of renal lesions. Opinion differs as to the relative value and danger of cystoscopic, pyelographic and intravenous urographic examination. The argument against cystoscopic and pyelographic procedure in cases of renal injury is the possibility of introducing infection into a fertile bed of traumatized tissue and of increasing the hemorrhage. Some urologists advocate intravenous urographic examination, but the disadvantage in its use is that the roentgen findings cannot be depended on to portray the actual traumatic lesion, because the secretory powers of the kidney are reduced or inhibited by trauma. Experimental and clinical trial has proved in general that retrograde pyelographic study is the more useful and dependable procedure for the early diagnosis of severe injuries to the kidney.

In all cases in which there is no severe bleeding from the kidney and no demonstrable injury to other organs, a waiting policy is the

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14 Peacock, A. H. Rupture of the Kidney. *West. J. Surg.* **48** 129-134 (March) 1940

15 Farman, F. Diagnostic and Operative Factors in Traumatic Rupture of the Kidney, *J. A. M. A.* **114** 210-216 (Jan 20) 1940



procedure of choice. Rest in bed, application of an ice bag to the side and administration of morphine constitute the treatment to be employed. Urologists are not at all in unanimous agreement as to the indications for operative intervention, mainly, in Farman's opinion, because of the difficulties of correct interpretation of clinical and urographic data. Early surgical exploration and repair are advocated by many because of the high mortality rate of rupture of the kidney. Nephrectomy is indicated by extensive destruction of tissue, multiple deep lacerations, injury to the pedicle, irreparable tears of the pelvis or ureter or persistent hemorrhage.

Some injuries of the kidney treated by expectant or conservative surgical methods require secondary nephrectomy if complicating sequelae follow, such as persistence of a urinary sinus, formation of a perirenal abscess or incapacitating chronic pyelonephritis.

Harrison<sup>16</sup> reported 27 cases in which patients suffered from renal trauma. In each instance injury had been caused by direct application of force over the kidney.

Hematuria is the cardinal sign of injury to the kidney of a patient who has recently sustained an accident.

Conservative treatment yields good results. There is a tendency for spontaneous improvement to occur, because of the processes of natural repair. The absolute indications for operation are persistent hemorrhage, extravasation of urine and renal infection. There was no mortality in Harrison's series.

Because of the possibility that congenital or acquired lesions of the kidney may antedate the trauma, thorough studies of the uninjured kidney as well as of the traumatized organ must precede operation.

Prather<sup>17</sup> evaluated certain observations and diagnostic procedures in the care of patients having renal injuries, differentiating those cases in which palliative measures will suffice from those in which surgical intervention is necessary.

The important clinical points which appear to place the condition in a group known as "contusions of the kidney needing only palliative treatment" are

1. No evidence of shock (90 per cent of cases)
2. No decrease in blood pressure during the first forty-eight hours of hospitalization
3. No increase in pulse rate in 90 per cent during the first two days in the hospital

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16 Harrison, J. H. Trauma to the Kidney, *Surg., Gynec. & Obst.* **70** 93-104 (Jan.) 1940

17 Prather, G. C. Traumatic Conditions of the Kidney. *Clinical Observations*, J. A. M. A. **114** 207-210 (Jan. 20) 1940

4 No increase in tenderness of the flank or of the abdomen during a forty-eight hour period after admission to the hospital

5 Visualization of the injured kidney in a high percentage of cases, although secretion of dye injected intravenously may be delayed or diminished

For those patients who have true rupture of the kidney and who do not die immediately from shock or hemorrhage, the following points seem pertinent. The most important clinical observation, which should be made by the same physician, is frequent examination for increasing tenderness and spasm in the lower abdominal quadrant of the injured side and evidence of spasm of the psoas muscles as evidenced by voluntary flexion of the hip. These features, Prather stated, indicate perirenal hemorrhage or extravasation of urine and are present even before there is any change in pulse rate or blood pressure. Use of intravenous pyelographic measures has been Prather's routine. Lack of visualization of the injured kidney is important and indicates the presence of a pathologic process requiring surgical treatment. Visualization of the kidney by means of intravenous pyelographic study does not rule out injury deserving surgical treatment. The choice between nephrectomy versus surgical repair of the injured kidney must be left to the experience and discretion of the operator. The condition of 1 patient who had traumatic severance of the renal pedicle and who lived for four days is described. Microscopic examination of the kidney of this patient indicated general infarction, but a thin rim of viable cortical tissue was present to a depth of 1 mm just below the renal capsule, apparently kept alive by capsular vessels.

*Perinephritic Abscess*—Vergoz and Lenck<sup>18</sup> made a study of anterior perinephritic phlegmon, with special reference to diagnosis and treatment of the condition. The diagnosis is particularly difficult because of the deep localization of such an abscess and because of the deceptive-ness of its symptoms, which frequently cause it to be mistaken for retrocecal appendicitis and other suppurative abdominal conditions. Its relative rarity in comparison to the classic posterior perinephritic abscess also misleads, so that the diagnosis is most frequently made only at operation. A history of furunculosis, panaris or traumatism, is of importance in directing the diagnosis toward perinephritic abscess, and roentgen examination may then confirm its anterior localization. Excessive elevation of the dome of the diaphragm and its immobility during respiration are signs that have been pointed out by certain authors.

Intravenous urographic study, especially, may show the contours of a tumor and its relation to the kidney.

18 Vergoz and Lenck. Du phlegmon perinephretique anterieur, *J durol* 47 369-394 (Mav) 1939

When the diagnosis cannot be made beyond the fact of the presence of an inflammatory tumor beneath the liver or near that organ and yet the possibility of an anterior perinephritic abscess is thought of, the only proper approach is the anterior route, with use of a transverse incision such as is made for surgical conditions of the liver and bile ducts. Exploration will then reveal the subperitoneal lesion in the region deep below the liver, where the posterior parietal serosa will be found to be red and edematous, with or without subjacent suppuration. The surgeon may then follow either of two courses: (1) closure of the peritoneal cavity, prolongation of the transverse incision toward the lumbar region and attack on the lesion by the subperitoneal route and by separation of the serosa (Bazy's method) or (2) walling off of the subhepatic region carefully with compresses and direct incision into the purulent collection. The second method is preferred by the authors as being simpler for patients already toxic from the effects of the abscess. In such cases a counterincision must be made in the lumbar region for drainage by gravity, while a Mikulicz drain (anterior) protects the peritoneum.

When the diagnosis of perinephritic abscess has been made but the location is uncertain, intervention should be made by the lumbar route. When this reveals only diffuse inflammatory edema, without the least sign of a purulent collection, the surgeon should never under any circumstances try to reach the anterior surface of the kidney with the finger and so gain access to the abscess, the danger to the peritoneum in such a procedure is too great. He should, rather, perform débridement of the internal lip of the lumbar incision and then make at its upper end an incision perpendicular to the primary incision, the peritoneum is thus separated and pushed back, and the prerenal suppurating cavity is opened. The surgeon can then easily transform the lumbar route into a lumboabdominal route, making it possible to reach with certainty the external margin of the kidney and its anterior aspect without touching the organ and without exteriorizing it.

When the diagnosis is correctly made before operation, the surgeon should strictly avoid the classic lumbar route, since it exposes only the lower part of the convex border of the kidney, and attempts made in this way to reach the upper pole are attended by great danger. The proper approach is the paraperitoneal route, with use of the anterior transverse incision of Bazy, this not only offers a more convenient position of the subject but leads directly to the anterior surface of the kidney and easily permits exploration of its entire contour.

The authors presented abstracts of 15 cases collected from the literature, to which they added 1 case of their own.

*Gumma*—Hunter<sup>19</sup> reported a case of gumma of the kidney. The patient was a 53 year old man who had lost 25 pounds (11 Kg) in the previous two years. The patient readily recovered after nephrectomy. The kidney weighed 2,265 Gm. The ureter was thickened and dilated. On section a lobulated, grayish yellow, extremely mottled, relief-map-like cut surface presented, with large, lobulated grayish yellow masses of the consistency of a myoma situated about the cortical portion of the tumor, while the central portion had a more grayish white, somewhat mottled fibrotic appearance. There was almost complete replacement of the renal parenchyma by the growth, which, generally speaking, was fairly well encompassed within the capsule except at the lower anterior pole, where it seemed to infiltrate the peritoneum and the perirenal fat. At the lower pole there was a cyst the size of a hen's egg, filled with a brownish yellow fluid rich in cholesterol crystals, the calices were markedly distorted, the superior one appearing rather dilated. The perivascular infiltrations, diffuse and focal infiltrations consisting chiefly of lymphocytes but also of numerous plasma cells, were seen throughout, and the picture seemed unquestionably that of a gummatous process.

Large syphilitic gummatous tumors are rare, and they are seldom diagnosed before operation. Microscopically, the lesion shows lymphocytic infiltration of plasma cells, with portions of necrosis and proliferation of connective tissue. It is not limited to the kidney but tends to infiltrate adjacent structures.

*Atrophy*—Marion<sup>20</sup> defined an atrophic kidney as a kidney which, for any reason, is of reduced size, is very different from the normal kidney and, as a rule, has an anatomic constitution that is equally abnormal. Atrophic kidney may be congenital or acquired.

When congenital, the atrophy constitutes an actual malformation, comparable to the absence of a kidney. Congenital atrophic kidney represents an arrest of development during embryonic life. The kidney varies in size from that of a pea to that of an apricot. It is by study of the pelvis and calices that the urologist can determine whether the condition is congenital or acquired. In congenital conditions these excretory structures are never normal in their arrangement, being reduced either in size (barring hydronephrosis) or in number. The internal arrangements are, however, very variable, the parenchyma may be wholly normal, or it may be normal in portions, with sudden transition to fibrous tissue, or, again, there may be inflammatory or sclerotic lesions. In some cases the renal mass is composed entirely of excretory tubules, with entire absence of glomeruli.

19 Hunter, A. W. Gumma of Kidney, *J. Urol.* **42** 1176-1178 (Dec.) 1939

20 Marion, G. Reins atrophiques, *J. d'urolog.* **47** 5-24 (Jan.) 1939

Acquired atrophy, which is much more frequent, is caused by either infection or infarct. In nearly all cases it is caused by the former. The infection may be simple chronic pyelonephritis, or it may be referable to the presence of a foreign body (calculus or an intrarenal drain). It is never produced by tuberculosis unless some common infection is associated therewith. Atrophy caused by infarct is generally partial, for when an infarct is produced by obliteration of the great vessels surgical intervention is, as a rule, very prompt. In cases of total acquired atrophy, in addition to diminished size of the organ, the surface presents furrows, and on section the parenchyma is markedly diminished in thickness and is irregular both in surface and in color. Histologic examination reveals destruction of the normal elements of the kidney.

These atrophic kidneys frequently are absolutely silent, with no symptoms to indicate their presence. When symptoms do appear, there is nothing characteristic about them. The diagnosis is made in some cases by roentgenogram, which shows the presence of a stone, after which the atrophy is revealed at operation. In other cases the results of separate catheterization of the two ureters will give the required information, in such cases the atrophic kidney will betray its presence by deficient function as compared with the other kidney, especially with reference to the amount of urine excreted. The results of catheterization, taken together with the pyelogram, usually will be sufficient to confirm the diagnosis. Acquired atrophy will be recognized by renal deficiency associated with an absolutely normal pyelogram, whereas congenital atrophy will exhibit renal deficiency associated with a tiny pelvis and a diminished number of calices, in some cases only a single calix being present.

The prognosis is without gravity in itself, but, since a kidney of this type causes a condition equivalent to complete absence of a kidney, its presence is of greatest importance when a decision is to be made with reference to the other kidney, contraindicating its removal under any circumstances. Treatment consists in removal of the atrophic kidney if it gives any symptoms that are painful. If it continues to be silent, it may safely remain in its place indefinitely.

#### URETER

*Calculus*—Thompson and Kibler<sup>21</sup> stated that ureteral calculi will pass spontaneously in about one third of the patients encountered, for approximately the same number, transurethral methods of extraction are justified and advisable, for the remaining third, ureterolithotomy or some other open surgical method seems best.

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<sup>21</sup> Thompson, G. J., and Kibler, J. M. Treatment of Ureteral Calculus, with Particular Reference to Transurethral Manipulation, *I A M A* **114** 6-11 (Jan 6) 1940.

Ureteral stone extractors, if carefully used, will be of distinct aid in removing the stone at the time of manipulation. If the condition is suitable for the use of a metallic stone extractor, this instrument will readily enter the ureter and quickly engage the stone. Repeated attempts to engage the stone should be avoided, for they will usually result in ureteral trauma and lead to complications.

The morbidity following proper transurethral methods is slight, and the mortality is extremely low.

In the large majority of cases the opinion of a urologist should be obtained before a decision is made as to the course of treatment for a patient who has ureteral calculus.

Alyea<sup>22</sup> said that overemphasis has been placed on the invention of special instruments for the extraction of ureteral calculi and that perhaps the simplest, safest and most efficient methods have been overlooked. He stated the opinion that the multiple catheter method is both efficient and safe, it includes the principles of dilation, lubrication of the ureter and grasping of the stone in the mesh of twisted catheters. To this technic Alyea added the idea of continuous constant traction on the engaged calculus, followed by relaxation of the ureter by production of spinal anesthesia at the time of extraction. Once the stone is caught, constant traction is obtained by means of rubber bands taped to the twisted catheters and attached to a perineal traction cage. Olive oil is injected through the catheters several times, and, if the stone has not come out in twelve to twenty-four hours, spinal anesthesia is produced and the catheters are withdrawn. Many of the larger stones have been extracted in this manner. An objection often raised to cystoscopic removal is that the calculus remaining in the lower part of the ureter for some time causes irreparable damage to the kidney. Many cases have been observed in Alyea's clinic which disprove this contention. In a series of 400 cases of ureteral stone recorded at the clinic, the stones in 71 per cent were removed cystoscopically, and the mortality was zero in these 296 cases. Alyea said that he has used the various ureteral scissors, fulguration fins and the like for cutting the ureteral meatus. The Collings knife used through a panendoscope probably is the most satisfactory. It is introduced and turned so that the blade points anteriorly. After the intravesical portion of the ureter has been elevated with the blade, the surgical cutting current is touched, and the knife cuts through quickly. The surgeon is sure not to cut too deeply with this method. It is remarkable how meatotomy may start stones moving even though they may be 2 or 3 cm from this region, Alyea stated that he has seen this occur many times.

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<sup>22</sup> Alyea, E. P., in discussion on Thompson and Kibler<sup>21</sup>

Bumpus<sup>23</sup> stated that the question of what method shall be used in the treatment of calculi in the ureter has much in common with the question of what method shall be employed in treating benign prostatic hypertrophy. With both conditions the urologist's judgment is often unduly influenced by the desire of the patient to avoid a major surgical procedure. Bumpus expressed doubt that this state of affairs ever occurs more frequently than in the treatment of stones in the ureter. It is imperative to acquaint the patient with the possibilities of serious complications occurring as a result of manipulative procedures and to obtain his consent for immediate major surgical intervention should such complications occur. Such complications result from three causes. The first and most important is urinary obstruction, the second, ureteral trauma with its associated periureteritis, and the third (and least frequent), perforation. The possibility of occurrence of any of these three complications is minimized by avoiding the use of steel instruments and employing only catheters for manipulative procedures. The catheters insure the continued passage of urine if obstruction should occur. They produce the least amount of trauma, and it is difficult if not impossible to produce ureteral perforation with them. They have, moreover, the added advantage of being readily accessible for removal singly if the manipulator is unsuccessful, whereas, in the case of the mechanical instruments, if a stone gets caught crosswise neither the instrument nor the stone can be recovered without resort to some major surgical procedure.

Foley<sup>24</sup> stated that the decision between expectant treatment and manipulation or open operation in the case of a stone in the lumbar portion of the ureter presents an entirely different problem from that involved in the same decision in the case of a stone in the pelvic portion of the ureter. Pelvic ureterotomy is always a rather formidable procedure, beset by the usual hazards of major surgical operations. Accordingly, when the stone is situated in the pelvic portion of the ureter, a major operation of this sort usually should be avoided in favor of expectant treatment and manipulation. This is not the case when the stone is in the lumbar portion of the ureter. The usual form of lumbar ureterotomy is also distinctly a major operation, but it can and should be almost a minor one. When the choice is between this improved form of lumbar ureterotomy or expectant treatment and manipulation, there is in most cases very little to recommend the latter. The choice between expectant treatment and manipulation or open operation should be dictated by only one thing—the welfare of the patient. To attain this, the surgeon must consider the risk of mortality,

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23 Bumpus, H. C., Jr., in discussion on Thompson and Kibler<sup>21</sup>

24 Foley, F. E. B., in discussion on Thompson and Kibler<sup>21</sup>

the risk of morbidity (irreparable pathologic change), the period of disability and the discomfort to be endured. In respect to all these, when the stone is first discovered in the lumbar portion of the ureter, the advantage lies entirely with a new form of lumbar ureterotomy devised by Foley and not with expectant treatment and manipulation. When a stone or anything of truly minute size is first discovered in the lumbar portion of the ureter, the patient's welfare will be served best by its immediate removal by this method of open operation. In such cases it is no trouble to start expectant treatment and manipulation, but how much trouble will ensue before success or failure results is another question. The patient will be obliged to endure at least a few attacks of colic. One or two or even three or four cystoscopic manipulations may be necessary, and they are a real hardship to the patient.

O'Connor<sup>25</sup> stated that the success of lumbar ureterotomy depends on the fact that the stone remains in that portion of the upper part of the ureter which it occupied before the incision was made. Some 20 per cent of these "upper ureteral calculi" will ascend to the upper part of the ureter or to the renal pelvis after the patient has been anesthetized, especially with spinal anesthesia, and with use of any degree of the Trendelenburg position. This same change of position has occurred no matter what position the patient has assumed on the operating table.

Lazarus<sup>26</sup> stated that the use of extract of insulin-free pancreatic tissue for three years has convinced him that this substance possesses distinct merit as an aid in the treatment of ureteral obstruction resulting from spasm, which frequently accompanies infection caused by calculi, and ureteral occlusions accompanying both functional and inflammatory strictures of the ureter. It has also proved of value in the treatment of postcystoscopic renal colic. The use of pancreatic substance (Grant), while it possesses all the merits of insulin-free tissue extract no. 568, has the distinct advantage of causing no pain at the site of the injection. To obtain the maximal benefit of the substance, ureteral catheterization should be instituted five minutes after its injection. Systemic reactions have not been observed in any of the cases in which it was employed. The most likely mode of action of this preparation in relieving spasm of the ureteral musculature is its neutralizing effect on the pressor action of epinephrine, as was suggested by Wolffe.

*Ureterovaginal Fistula*—Ockerblad and Carlson<sup>27</sup> reported 5 cases of ureterovaginal fistula, in 4 of which the condition was caused by pelvic

25 O'Connor, V. J., in discussion on Thompson and Kibler<sup>21</sup>

26 Lazarus, J. A. Further Observations on Use of Insulin-Free Pancreatic Tissue Extract as an Aid in Cystoscopic Treatment of Impacted Ureteral Calculi and Spastic Occlusion of Ureter, *J. Urol.* **43** 102-107 (Jan.) 1940

27 Ockerblad, N. F., and Carlson, H. E. Surgical Treatment of Ureterovaginal Fistula, *J. Urol.* **42** 263-268 (Aug.) 1939



operations In the fifth it was referable to a ureteral calculus which had become impacted in the terminal 5 cm of the left ureter and which followed a very unusual course by eroding through into the vagina

A survey of the literature reveals scores of cases The cure is still either reimplantation or nephrectomy Reimplantation is done when possible, and nephrectomy is resorted to when the kidney is badly infected Ockerblad and Carlson expressed disagreement with the opinion expressed by European writers that this operation is useless and that the end result is destruction of the kidney There have been numerous cases in which the patient has lived longer than ten years in good health They stated that to leave a part of a kidney which is healthy and not infected is much better than not to leave any kidney

Patton<sup>28</sup> reported 16 cases of ureterovaginal fistula

The importance of early investigation is stressed, with application of appropriate therapeutic measures in an effort to preserve the kidney

A thorough urologic study is essential in every instance of leakage of urine through the vagina, even when a vesicovaginal or urethrovaginal fistula is obviously present

The type of therapy to be applied to ureterovaginal fistula should be determined only after careful study and should be directed primarily toward preservation of renal function and reestablishment of the urinary channel to approximately its normal state Nephrectomy should be reserved for the irreparably damaged kidney or as a measure of last resort

Dilation should be the first procedure In the event of failure ureteroureteral anastomosis is the method of choice for high ureteral injuries, and reimplantation into the bladder is the method of choice for low ureteral injuries

Patton described a method of reimplantation of the ureter into the bladder through the intramural portion of the ureter which reproduces the normal, and it should be applicable in a definite percentage of cases

*Transplantation*—Hess<sup>29</sup> stated that transplantation of the ureters into the bowel as an operative procedure should be considered only when a condition exists which makes life so miserable that death is usually to be preferred The operation, even with the simplest efficient technic in the hands of the most skilful surgeons, is not without a very high mortality and morbidity It is rarely indicated in cases of cancer of the bladder and vesicovaginal fistula It is more frequently indicated for

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28 Patton, J F Ureterovaginal Fistula A New Method of Reimplantation of the Ureter into the Bladder, *J Urol* **42** 1021-1032 (Dec) 1939

29 Hess, E Transplantation of the Ureters, *Am J Surg* **45** 479-498 (Sept.) 1939

the contracted bladder that has resulted from the healing of tuberculous cystitis, and with this class of condition there results a low mortality, with satisfactory symptomatic results. The procedure is also indicated in cases of intractable and incurable interstitial cystitis. It is a valuable procedure in cases of exstrophy of the bladder and epispadias but should never be used for exstrophy in the adult patient without a complete explanation to the patient of both its mortality and its morbidity, and it should be an operation elected by the patient.

*Dilatation*—In a study of the ureteral dilatation of pregnancy, van Wagenen and Jenkins<sup>30</sup> stated that excretory urographic studies have shown that dilatation of the upper portion of the urinary tract occurs in the pregnant rhesus monkey.

Of the 6 pregnancies with which pyeloureteral dilatation was present, 1 was allowed to proceed without interruption, and the markedly dilated urinary tract returned to normal in seven days.

In 3 instances fetuses were removed after the dilatation had reached a high degree, and the dilatation was sustained or increased during the time the placenta remained in situ. After expulsion of the placenta the dilatation of the ureters always decreased, returning to normal size in every case in which the course was uncomplicated by infections.

The most convincing data concerning the primary importance of the hormonal influences of pregnancy in bringing about dilatation were those concerning 2 pregnancies in which the fetuses were removed on the seventy-fourth and the seventy-first day of gestation respectively. In the first animal beginning ureteral dilatation was found in the latter half of the fifth month, fifty-nine days after removal of the fetus. This dilatation increased considerably during the sixth month. The placenta was expelled on the one hundred and sixty-fourth day of gestation, after which dilatation regressed. In the second animal dilatation appeared only in the sixth month of pregnancy, eighty-one days after removal of the fetus. The placenta was retained until the one hundred and fifty-first day of gestation, and both ureters returned to normal on the fourth day afterward.

Van Wagenen and Jenkins concluded that dilatation of the upper portion of the urinary tract can develop after removal of the fetus and while the placenta remains in a functional state within the uterus. It would appear, therefore, that this physiologic change is related primarily to the stage of pregnancy and secondarily to the influence of the increased weight of the uterus with its contents in pregnancy.

30 van Wagenen, G., and Jenkins, R. H. An Experimental Examination of Factors Causing Ureteral Dilatation of Pregnancy, *J Urol* 42 1010-1020 (Dec) 1939.

*Injury*—Ostling<sup>31</sup> described a case in which a ureter which during a pelvic operation had chanced to be severed 9 cm above the bladder was immediately sutured over a catheter brought out through the urethra. Eight and a half years later excretory urographic examination showed a normal renal pelvis on the damaged side. A constriction was revealed at the seat of the suture, and immediately above this the ureter was found to be slightly dilated. This constriction corresponded to a valvular formation, preventing catheterization and retrograde pyelographic procedures. Since the view held concerning the prognosis of ureteral suture is based on experiences encountered before urography came into use, according to which treatment in a case like that of Ostling would have been counted as a failure, and since the literature affords no binding proofs that the results are particularly bad, it does not seem unlikely that after-examination by urographic methods might bring about a reassessment of the functional capacity resulting from ureteral suture after transverse section.

Rusche and Bacon<sup>32</sup> stated that ureteral trauma occurs most commonly in the course of surgical procedures on the internal genitalia of the female, next as a result of cystoscopic intraureteral instrumentation or of external violence and finally as the result of the presence of foreign bodies.

The present increase in the incidence of ureteral injury is referable mainly to recognition of the pathologic lesion. Unquestionably the actual incidence is not known, because unilateral ligation of the ureter results in numerous instances in unrecognized destruction of the kidney.

Rusche and Bacon unqualifiedly recommended ureteral catheterization as the method of prevention of ureteral injury in surgical conditions that are considered preoperatively to be difficult.

The treatment of an injured ureter should consist of initiation of the procedures that will preserve, ultimately, the function of the ureter and kidney. Treatment is dependent on the time of recognition of the injury, the type and situation of the injury and the condition of the patient.

If complete ureteral division is discovered at the time of operation, ureterovesical implantation or ureteroureteral anastomosis is the procedure of choice if the operation will not be hazardous.

When a segment has been removed, ureterointestinal or ureterocutaneous anastomosis or ligation is recommended.

Bilateral ureteral occlusion, recognized postoperatively, requires bilateral nephrostomy. The procedure of deligation is to be condemned.

31 Östling, K. Zur Kenntnis der Spätresultate bei Naht des querdurchtrennten Harnleiters, *Acta chir. Scandinav.* **83** 74-82, 1939.

32 Rusche, C. F., and Bacon, S. K. Injury of the Ureter Due to Surgery, Intra-Ureteral Instrumentation, External Violence and Foreign Bodies. Report of Fifty Cases, *J. A. M. A.* **114** 201-207 (Jan 20) 1940.

Intraureteral instrumentation as a cause of ureteral injury is dependent usually on impaction of a calculus and adjacent disease of the ureter. The present increase in the incidence of ureteral perforation is related closely to the recent development of many devices designed to remove calculi.

#### PROSTATE GLAND

*Hypertrophy*—Abeshouse,<sup>33</sup> after a study of 200 consecutive transurethral resections and 234 prostatectomies, concluded that transurethral resection deserves a definite place in the operative treatment of prostatic obstruction. It is the operation of choice in cases of median bar, solitary median lobe and solitary subcervical hypertrophy. Excellent results also may be obtained in instances of small or moderate-sized enlargement of the median or lateral lobes. The operation affords palliative relief in cases of carcinoma in which there are obstructive symptoms, it provides an excellent method of removing obstruction caused by contractions, nodules or tags following prostatectomy, and it is valuable in cases of persistent suprapubic fistula. Abeshouse stated the belief that the operation is not suitable in cases in which "large bilobed or trilobed hypertrophy" with marked intravesical or intraurethral bulging is present.

Suprapubic prostatectomy is suitable for cases in which marked enlargement of the prostate gland is present, especially if this is accompanied with vesical conditions requiring operative treatment. The operation requires no unusual operative skill and insures a good and permanent functional result.

Perineal prostatectomy is an ideal operation for the treatment of large hypertrophy and small fibrotic glands with or without prostatic calculi. It is the only method offering a cure of early or concealed carcinoma. It requires greater operative skill and, when properly done, insures an equally good functional result. The fear of incontinence, impotence and fecal fistula is dispelled by complete mastery of the operative technique.

LeDuc<sup>34</sup> described a method by means of which the internal structure and distribution of the prostatic duct systems may be studied visually.

Anatomically, the prostate gland may be considered to be composed of two major lobes (the lateral lobes) and of a smaller median lobe, the latter may sometimes be replaced by a prespermatic commissure consisting of interlacing lateral lobe ducts.

33 Abeshouse B S. A Comparison of Results in the Treatment of Prostatic Obstruction by Transurethral Resection and Prostatectomy, *J Urol* 42 1101-1122 (Dec.) 1939.

34 LeDuc, I E. The Anatomy of the Prostate and the Pathology of Early Benign Hypertrophy, *J Urol* 42 1217-1241 (Dec.) 1939.

The situation of the orifices of the ducts may be correlated fairly accurately with the portion of glandular tissue drained by them

- 1 Those on the lateral urethral walls, in the prostatic sulci and on the verumontanum and inferior crista drain corresponding portions of the lateral lobes, laterally or obliquely-laterally, to the orifice of the duct
- 2 Those on the superior crista drain the median lobe or the tissue in the mediolateral commissure

Microscopic studies of the earliest lesions of benign hypertrophy offer confirmatory evidence in support of the theory promulgated by Reischauer and confirmed by Deming and Neumann that the essential lesion of prostatic hypertrophy is the nodular proliferation of fibrous tissue, in which glandular penetration and growth take place only as secondary phenomena

The glands taking part in the formation of prostatic hypertrophy appeared in this study to be entirely of the submucosal type

Smith<sup>35</sup> stated that prostatic obstruction may be caused by cancer, fibrosis or hyperplasia

Hyperplasia is believed by some authorities to develop only in the submucous glands of the urethra Others believe that it may also develop in the lateral lobes themselves

Experimental evidence seems to prove that in certain animals hypertrophy of the prostate gland is caused by deficient secretion of inhibin, a hormone secreted by the tubular epithelium of the testicle Doubt exists as to whether the type of hypertrophy so produced is analogous to the prostatic hyperplasia found in man, but the fact that hypertrophy develops only as the sexual function begins to wane makes it seem likely that this theory is the most probable of all that have been suggested

After therapy based on this hypothesis, definite improvement has been noticed in a majority of patients Equally good results have been claimed by a few urologists who have treated patients suffering from hypertrophy of the prostate gland by roentgen or radium therapy and also have been observed in a series of 93 patients who were not treated by operation, by irradiation or by glandular therapy

Smith reviewed the various methods of operative removal of the obstructing prostatic tissue In his opinion, transurethral resection is the best method for prostate glands which are not readily enucleable as is true in the majority of instances of prostatic cancer, small, fibrous prostate glands and small hypertrophy These cases constituted 41 per cent of a series of prostatic operations done in the last six years For larger hypertrophy, open operation is preferable Prostatectomy is not an obsolete operation

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35 Smith, G G The Obstructing Prostate Its Treatment, Surgical and Otherwise, *J Urol* 42 145-157 (Aug) 1939

*Cancer*—Wishard, Hamer and Mertz<sup>36</sup> presented a series of 224 cases of carcinoma of the prostate gland. Of these the patients in 148 were treated surgically (120 by resection) and 76 were treated nonoperatively. The average age was 65 to 70 years. The majority of the patients were hospitalized two to four weeks for prostatic resection.

Thirty-four per cent of the patients in the series could not be operated on, chiefly because of metastases to bones, symptoms too mild to necessitate operation, severe renal lesions and death which occurred before anything could be done. Two thirds of the patients not treated surgically died within the first year after the diagnosis had been established.

Patients sought relief primarily because of dysuria, vesical irritability and retention of urine. Almost half of the patients receiving surgical treatment had complete retention of urine before operation, about 75 per cent had less than 1 fluid ounce (30 cc.) of residual urine at the time of dismissal from the hospital.

The amount of tissue removed at resection in the majority of instances was less than that removed by resection for benign hypertrophy of the prostate gland. Multiple resections were required for about a fourth of the patients.

Rectal and cystoscopic examination disclosed grade 2 enlargement as the customary observation. A soft prostate gland was found by rectum in almost 10 per cent of the cases. Pathologic examination revealed that the condition of more than 10 per cent of the glands would have been erroneously considered benign if reliance had been placed entirely on clinical observations.

Roentgen examination revealed osseous metastases in 31 per cent of the patients examined. The fourth lumbar vertebra was the point of predilection.

In Wishard, Hamer and Mertz's experience the operative risk of resection has not been negligible. Seven per cent of the private patients and 15 per cent of the ward patients died after resection and before leaving the hospital. Death was referable almost exclusively to cardiac, pulmonary or renal causes. The total 'hospital death rate' for all patients, both those who underwent operation and those who did not, was 13 per cent for the private patients and 29 per cent for the ward patients. Forty per cent of the patients who underwent resection and who left the hospital alive were known to be dead within two years after their departure therefrom.

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<sup>36</sup> Wishard, W. N., Jr., Hamer, H. G. and Mertz, H. O. Transurethral Resection in Treatment of Carcinoma of Prostate, *J. Urol.* **42**: 1088-1109 (Dec.) 1939.

*Abscess*—Hammer and Thompson<sup>37</sup> reported a case of chronic prostatic abscess with these three considerations in mind (1) Chronic prostatic abscess is a comparatively rare complication of chronic prostatitis, (2) diagnosis may be difficult and may require intensive urethroscopic examination, and (3) the condition may be satisfactorily treated by transurethral operation. The patient was a man 31 years of age who presented a history of backache of increasing severity and perineal discomfort when sitting, so that he had been unable to work as a truck driver. He also had lassitude and recurring bouts of fever. Treatment elsewhere with urinary antiseptic agents had failed to clear pyuria and bacilluria (*Pseudomonas*) because of the presence of prostatitis grade 4. Administration of mandelic acid and local treatment, followed by tonsillectomy and administration of sulfanilamide, also failed. Urethroscopic examination revealed purulent material to be exuding from the dilated prostatic ducts and also from the ejaculatory ducts. The cavity of an abscess 3 cm in diameter was unroofed by the resectoscope, and the walls of this cavity were excised. The patient left the hospital in two days and voided clear urine five days later for the first time. The backache and perineal discomfort disappeared at the same time. Prostatic massage is contraindicated postoperatively. Surgical treatment is contraindicated in the ordinary case of diffuse chronic prostatitis.

*Prostatic Fluid*—Experimental studies by Barnes<sup>38</sup> have shown that human prostatic fluid contains a substance which has a definite pharmacologic action and which when administered in comparatively large doses is toxic. This substance was shown to exert a marked toxic effect when given to rats in doses of 1 cc intraperitoneally, and sometimes this dose reduced the activity of the animals almost to nil. No tolerance to this substance is developed by giving repeated increasingly large doses to rats, and small doses repeated daily have little, if any, cumulative effect. The most marked and constant pharmacologic action of this substance was found to be, experimentally, depression of blood pressure and marked stimulation of smooth muscle in vitro.

This experimental investigation shows that normal human prostatic fluid as obtained by prostatic massage has a definite, constant and marked pharmacologic action which is not identical with that of any other substance now known. Because of this definite action, prostatic fluid must have a function other than that which has been ascribed to it, that is, neutralization of the acid vaginal secretions, producing a more suitable medium for the life of spermatozoa. The action on smooth

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37 Hammer, H J, and Thompson, G J. Chronic Prostatic Abscess. Report of Case, Proc Staff Meet, Mayo Clin **14** 446-447 (July 12) 1939.

38 Barnes, R W. An Experimental Study of the Pharmacology of Prostatic Fluid, J Urol **42** 1207-1216 (Dec) 1939.

muscle would suggest that the substance has the function, after it is absorbed through the vaginal mucosa, of producing antiperistalsis in the uterus to aid in the dissemination of spermatozoa

#### BLADDER

*Tumor*—Vermooten<sup>39</sup> reported a case of rhabdomyosarcoma of the bladder. Such cases are very rare.

The patient was a girl aged 20 months. Because of retention of urine she was catheterized twice daily until five days later, when a portion of the tumor prolapsed into the urethra. The child was given a general anesthetic, presumably to reduce the prolapse, and died under anesthesia. At necropsy extensive bronchopneumonia was observed in both lungs. There were multiple abscesses in both kidneys. Associated with the pyelonephritis was mild bilateral hydronephrosis, with dilated, tortuous and infected ureters. The bladder contained a tumor which arose from a pedicle 1 cm long and 0.5 cm wide, overlying the trigon. It had the appearance of a large bunch of grapes and consisted of two main masses. The mass immediately connected to the pedicle had a diameter of about 7 cm and was 4 cm long. Attached to this mass by a very narrow pedicle was the main tumor mass, measuring 8 cm in length and at its widest point having a diameter of 5 cm. In addition to the main tumor mass there were two other portions adjacent to the pedicle, in which apparently new tumors of the same type were beginning to form.

The microscopic picture as described by the pathologist of the South African Institute for Medical Research "revealed that the lobules of the tumor were made up of cellular and myxomatous areas enclosed in coverings of transitional epithelium of normal type. In the cellular areas and scattered throughout the myxomatous tissue elongated fibres of striped muscle and large rounded acidophilic cells exhibiting a fibrillar cytoplasm and radial striation were seen."

Orr, Carson and Novak<sup>40</sup> presented a study of clinical results obtained in the treatment of malignant tumors of the bladder by 267 surgeons. An analysis of more than 26,000 cases of vesical carcinoma forms a basis for this discussion. This analysis was obtained through the medium of a questionnaire in an effort to ascertain the method of treatment which would give the patient the greatest degree of comfort and the longest life.

39 Vermooten, V. Rhabdomyosarcoma of the Bladder. Case Report, *J Urol* 42:126-130 (Aug) 1939.

40 Orr, L. M., Carson, R. B. and Novak, W. F. A Statistical Study of Present-Day Methods Used in the Treatment of Tumors of the Bladder, *J Urol* 42:778-788 (Nov) 1939.



For the sake of convenience, the questionnaire was divided into two sections, one, "Conservative Treatment," including all methods of treatment other than total cystectomy, and the other, "Radical Treatment," including only total cystectomy and ureteral transplantation. Of the two hundred and sixty-seven surgeons reporting, two hundred and twenty-one favored conservative methods of treatment, and only eight favored radical treatment, or total cystectomy. The conservative methods used have been set forth in detail.

Of all methods used in the treatment of tumors of the bladder, fifty-one surgeons considered segmental resection of the bladder to be the one which would afford the patient the most comfort and the longest life.

Three hundred and fifty-three cases of total cystectomy and ureteral transplantation have been collected. An average mortality rate of 33.2 per cent attended the operation. Ninety-two patients died during the first year. Eighteen patients had lived more than five years at the time Orr, Carson and Novak wrote, although the majority of the operations had been performed during the five years prior to the time of writing.

The reasons for not performing total cystectomy as given by fifty-seven surgeons were that the operation is too radical and the mortality rate too high. Sixty-six stated that the patients when seen were too old, the disease was too far advanced, or renal damage had already occurred, nine cited difficulties in convincing patients and the referring physician, fourteen stated that cystectomy should be performed more often in suitable cases, and twelve admitted that they did not have enough surgical experience.

This study has definitely brought out again the necessity for early diagnosis in instances of cancer of the bladder. Education not only of the laity but of the general practitioner should be continued according to methods which will result in earlier examination by the urologist of patients who have symptoms of tumor of the bladder.

Metastasis to regional lymph nodes and distant organs is probably more rapid than has heretofore been assumed.

Lowrey<sup>41</sup> reported 5 cases of adenocarcinoma of the bladder, 3 of the 5 lesions were situated in the dome, and the remaining 2 in the base of the bladder. These tumors showed three gradations of malignancy. One tumor was relatively benign, and both adenoma and adenocarcinoma were found in the same growth. Two tumors showed a moderate degree of malignancy, the patient had been comparatively well during a three year period. Two other tumors were of the rapidly growing type and secondary growths were found to involve the regional and iliac lymph glands a short time after the onset of symptoms.

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<sup>41</sup> Lowrey S R. Adenocarcinoma of the Bladder, *J Urol* **42** 118-125 (Aug) 1939.

Shivers and Henderson,<sup>42</sup> in a discussion of a group of 101 cases of tumor of the bladder, stated that 19 of 32 patients presenting tumors with narrow attachments to the wall of the bladder are living and that none, so far as the authors know, have died of the disease. The longest interval has been fourteen years. Five died from other causes, and the authors were unable to communicate with 8. All of the patients were treated by surgical diathermy, either transurethrally or transvesically.

In a group in which the tumors showed a wide attachment to the wall of the bladder, there were 35 cases. Fifteen patients were dead as a result of the disease, 4 died from other causes and contact could not be made with 9. Only 7 in this group heard from were still living at the time of writing. One patient had survived for seven years with a bladder apparently normal on examination.

In the group of 34 cases of infiltrating carcinoma, all but 2 of the patients are now dead. These patients received high voltage roentgen and radium treatment with or without surgical treatment. The 2 surviving patients had lived, at the time Shivers and Henderson wrote, eight years after the transvesical implantation of radon.

The importance of careful follow-up treatment cannot be overemphasized. It is Shivers' and Henderson's custom, they stated, to use cystoscopic methods for these patients at monthly intervals for the first year and as often thereafter as they deem it necessary.

Transurethral resection has a very important place in the treatment of vesical tumors of the pedunculated type if they are suitably situated.

Shivers and Henderson have not resorted to any radical surgical procedure in the treatment of tumors of the bladder, because most of their patients who presented extensive involvement of the wall of the bladder were poor risks. They stated the belief that when cancer of the bladder has developed to a point at which less radical means of treatment cannot be used, the possibility of performing cystectomy has usually passed because of the poor physical condition of the patient which is the result of urinary sepsis, secondary anemia or renal insufficiency. The authors stated that they feel justified under such conditions in choosing a procedure which will prolong the patient's life in as much comfort as possible, rather than in attempting a cure.

Kickham and Jaffe,<sup>43</sup> in discussing the upper portion of the urinary tract in the presence of tumors of the bladder, stated that there is a marked tendency of vesical growths to be situated in proximity to the ureteral orifices. They emphasized the high incidence of pathologic

42 Shivers, C. H. de T. and Henderson, K. P. Tumors of the Bladder. A Review of One Hundred and One Cases. *J. Urol.* **42**: 761-777 (Nov.) 1939.

43 Kickham, C. J. E. and Jaffe, H. L. The Upper Urinary Tract in Bladder Tumors. *J. Urol.* **42**: 131-139 (Aug.) 1939.

changes, obstructive and septic, in the upper portion of the urinary tracts of patients with malignant disease of the bladder

They stated the belief that it is of paramount importance to determine the status of the upper portion of the urinary tract prior to the institution of treatment (so that patients who have ureteral occlusion may be properly managed) Measures for prophylaxis are recommended in the absence of ureteral obstruction to insure adequate renal drainage in the event that acute or delayed obstructive changes occur

The end results in the management of tumors of the bladder will be materially improved if death from renal insufficiency is prevented The proper drainage of obstructed kidneys may secure relief from distressing symptoms and prolong the life of those patients in whom the status of the disease in the bladder offers a hopeless prognosis

*Diverticulum* —Thompson, Kermott and Cabot <sup>44</sup> stated that diverticulum of the urinary bladder is of congenital origin and that it generally causes no symptoms until obstruction develops at the vesical outlet, the obstruction usually is caused by benign prostatic hyperplasia but may be the result of contracture of the vesical neck, congenital obstruction or prostatic carcinoma

If the obstruction at the vesical outlet is to be removed by suprapubic operation, it is best to precede this operation by diverticulectomy, performed generally as a first stage procedure

In the large majority of instances thorough transurethral resection of the tissue obstructing the vesical neck will relieve the patient's symptoms, and diverticulectomy will not be required If the symptoms are not satisfactorily relieved, diverticulectomy can be performed subsequent to transurethral prostatic resection, the latter operation in no way adds to the technical difficulty of removing the diverticulum

An analysis of the results obtained in 96 patients who were treated only by transurethral resection of the obstruction at the vesical neck warrants the conclusion that in patients of the age group likely to have prostatic disorders the risk, discomfort and prolonged hospitalization incidental to diverticulectomy can almost always be avoided

*Cystitis Cystica* —Craig <sup>45</sup> stated that cystitis cystica glandularis is a response of the mucous membrane of the bladder to chronic irritation The evidence does not indicate that the glands are necessarily the result of embryonal misplacement of intestinal epithelium The condition probably develops by means of a process of metaplasia of the epithelium,

44 Thompson, G J, Kermott, L H, and Cabot, H The Management of Diverticulum of the Bladder Ninety-Six Patients Treated by Transurethral Prostatic Resection Surg, Gynec & Obst **70** 115-119 (Jan) 1940

45 Craig L G Cystitis Cystica Glandularis, J Urol **42** 1197-1203 (Dec) 1939

passing through the stages of the cell nests of Brunn, cystitis cystica and, later, cystitis glandularis. The formation of glands appears to involve an active secretory process in the cells rather than a mere degeneration of the central cells of the Brunn's nests. Cystitis cystica glandularis is potentially, but not actually, malignant and may be the point of origin of adenocarcinoma of the bladder.

*Tabetic Changes*—Emmett<sup>46</sup> stated that disturbance of vesical function constitutes one of the most aggravating symptoms of tabetic cord bladder. It usually is described in textbooks on neurology as "difficulty in urination, urinary retention and incontinence." As a matter of fact, true incontinence in the presence of *tabes dorsalis* is not common. In most instances so-called incontinence, if carefully studied, will be found to result from overflow from a distended bladder or from urgency referable to infection of the urinary tract which has been initiated by the retention of urine.

The diagnosis of cord bladder usually has been based on the cystoscopic observations which follow reduction in expulsive force of the bladder, trabeculation, relaxation of the vesical neck (the internal vesical sphincter) and diminution in sensation. In a large number of cases the atonicity and trabeculation of the bladder were the only observations apparent. In reality, therefore, the diagnosis of tabetic cord bladder in such cases simply indicated the presence of an atonic bladder with retention of urine, occurring in the presence of *tabes dorsalis*. That the tabetic condition was responsible for the vesical disturbance was only surmised. When such a system of diagnosis was employed, retention of urine in many cases was diagnosed as "cord bladder," whereas, if the truth were known, the condition was entirely unrelated to the neurologic disease.

Newer concepts of the physiologic aspects of micturition suggest that the act of micturition results from the contractile response to stretch of muscle fibers of the bladder.

In recent years transurethral resection has been performed at the Mayo Clinic for a group of patients with such symptoms, with exceptionally good results. The former fear of postoperative incontinence is no longer present, since it is known now that if no true incontinence exists before operative intervention there will be none afterward if the external sphincter (compressor urethrae muscle) has not been injured. Resection of the vesical neck in a case in which the obstruction is extremely minimal (such as a very slight contracture) will often restore perfect vesical function even in cases in which a large amount of residual urine has been present. Also, the observation is made that many con-

46 Emmett, J. L. "Tabetic Cord Bladder." Newer Concepts in Diagnosis and Treatment, Proc. Staff Meet., Mayo Clin. 15: 91-96 (Feb. 7) 1940.

ditions which formerly were diagnosed as "tabetic cord bladder" are in reality simple obstruction of the vesical neck in which the associated *tabes dorsalis* plays little, if any, part. Combinations of various degrees of obstruction of the vesical neck and neurologic involvement make diagnosis interesting.

Emmett reported several cases, in 1 of which a man aged 63 years underwent neurologic examination, which revealed observations typical of *tabes dorsalis*. There was retention of 1,500 cc of urine. Eight grams of tissue was removed by transurethral resection, after which the patient was able to empty his bladder completely. This was an instance of true tabetic cord bladder associated with mild obstruction of the vesical neck.

*Malakoplakia*—Rudnick and Ragins<sup>47</sup> reported a case in which a white woman 53 years old had malakoplakia associated with chronic ascending unilateral pyelonephritis, nephrolithiasis and chronic ureteritis. The plaques were composed of large polygonal cells containing Michaelis-Gutmann bodies and also large accumulations of lymphocytes and plasma cells. The cells were entirely distinct from those of the transitional epithelium covering them, as was shown by various differential stains.

Bacteriologic studies revealed the chief organism to be *Bacillus mucosus capsulatus* (Friedlander's bacillus), which was isolated from the urinary bladder and from the left ureter.

On removal of the left kidney and ureter all the symptoms and the malakoplakia disappeared.

*Drainage of Prevesical Space*—Chute<sup>48</sup> discussed drainage of the prevesical space. Because of the fascia which covers the muscles that form the urogenital pelvic diaphragm there is no way in which the prevesical space can drain itself. Infection tends to remain and to spread because of the loose, fatty tissue. Consequently, if the space is not drained or if the drain is removed too early a poorly drained septic pocket is left, resulting in a slowly healing wound or in formation of an abscess. In Chute's opinion, extensive suppuration in this space accounts for some of the instances of pericystic infection, periostitis or even osteomyelitis of the pubic bone. He cited 2 cases in which complications resulted from premature withdrawal of the drain. He stated that withdrawal of the drain should not be started until six days have elapsed and until the temperature has returned to normal and that the drain should then be shortened daily.

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47 Rudnick, D F, and Ragins, A B. Malakoplakia of the Bladder, *J Urol* **42** 108-117 (Aug.) 1939.

48 Chute, R. A Note on Drainage of the Prevesical Space, *New England J Med* **220** 108-109 (Jan 19) 1939.

*Rupture of Inflammatory Masses into Bladder*—Falk and Hochman<sup>49</sup> stated that spontaneous rupture of prostatic or pelvic abscess into the bladder occurs

The symptoms and signs are usually masked by the underlying pathologic process. Rupture of a pelvic inflammatory mass into the bladder is usually shown by the sudden appearance or marked increase of pus in the urine, with severe "urinary symptoms," such as frequency of urination, burning and tenesmus. Such symptoms are very significant if they are followed by improvement in the patient's condition and recession of temperature.

Cystoscopic study establishes the diagnosis, revealing an area of bullous edema from the center of which pus exudes.

The fistula usually heals spontaneously, recession of the mass being achieved by medical treatment or by surgical intervention.

Patients who come for gynecologic treatment with a pelvic mass should have routine investigation of the genitourinary tract, including cystoscopic study, because the presence of local edema of the vesical mucosa from a contiguous inflammatory mass may be a premonitory sign of perforation.

Three cases of rupture of a pelvic infection into the urinary bladder, with a collection of 21 cases from the literature, are reported.

#### URETHRA

*Infection*—In a series of 40 cases of sulfanilamide-resistant gonorrhea reported by Alyea and Daniel,<sup>50</sup> 55 per cent of the patients were cured with sulfanilamide. Sulfanilamide probably has a greater specificity for certain strains of gonococci. Smaller daily doses than were formerly advocated are effective. The interrupted method of administration is recommended. To wait for therapeutic maturity is not recommended as a routine procedure. Clinically, sulfanilamide is more easily tolerated than is sulfanilamide. Peripheral neuritis was the only serious toxic reaction encountered, and it occurred once in this series of 40 cases.

Johnson, Leberman, Pepper and Lynch<sup>51</sup> noted the results of a follow-up study in which 63 of 80 male patients suffering from gonorrheal urethritis were treated with sulfapyridine. Of these 63 patients, 50 (79.2 per cent) passed all the tests of cure, the average duration of

49 Falk, H. C., and Hochman, S. Rupture of Pelvic Inflammatory Masses into the Urinary Bladder, *Am J Obst & Gynec.* **38** 654-651 (Oct.) 1939.

50 Alyea, E. P., and Daniel, W. E. Treatment of Sulfanilamide-Resistant Gonorrhea with Sodium Sulfanilamide, *J Urol* **42** 864-873 (Nov.) 1939.

51 Johnson, S. H., Leberman, P. R., Pepper, D. S. and Lynch, H. Use of Sulfapyridine in the Treatment of Gonococcal Urethritis in the Male. *Am J M Sc* **198** 594-602 (Nov.) 1939.

discharge in these cases being two and seventy-seven hundredths days. The dose was 3 Gm of sulfapyridine a day for four days, followed by 2 Gm a day for six to ten days. In a group of 19 patients whose condition had been resistant to previous treatment with a sulfanilamide derivative, 68.4 per cent were cured with sulfapyridine administered thereafter. Forty-five patients (56.2 per cent) had one or more toxic reactions. Values for sulfapyridine in the blood were of no significance in prophesying reactions or cures. In the authors' experience, sulfapyridine has been the most efficient sulfanilamide derivative in the treatment of gonococcic urethritis in the male.

*Abscess*—Schmitz and Nelson<sup>52</sup> reported 8 cases of suburethral abscesses, urine pockets and diverticula in the female urethra. More than 100 cases of diverticulum of the female urethra have been reported. Many names are applied to the disorder—"urethrocele," "cyst," "abscess," "urinary pocket" or "urinary pouch." However, the three previously mentioned conditions should not be confused with abscesses or cysts of Skene's glands, vaginal cysts or small vaginal myomas. Urethral diverticula may be classified as either true or false. When all the layers of the urethra are involved in the process, they are called "true diverticula." False diverticula are those in which only the submucosa and mucosa protrude, the muscularis having ruptured.

The symptoms produced by urethral diverticula are directly referable to the genitourinary tract. Pain, frequency of urination and burning are nearly always present in this condition, but involuntary loss of urine is the most annoying symptom and is rather constant. Passage of bloody urine is an associated symptom in a few cases. Swelling noticeable to the patient is an infrequent symptom. The diagnosis of urethral diverticula is based on careful examination of the urethra and vagina. A history of urinary difficulty associated with involuntary soiling, together with the discovery of a collapsible bulge in the vagina over the urethra, leads to the suspicion of diverticulum. If urine can be expressed from the mass into the urethra after the bladder has been emptied by voiding or catheterization, the diagnosis is made even without visual intraurethral examination. The diagnosis is absolute after direct visualization of the diverticulum opening on urethroscopic examination. The pocket also may be filled with opaque material and then examined by roentgen rays. Skene's abscesses are excluded by reason of their situation. Solid tumors or cysts do not collapse under pressure.

The treatment of choice for this deformity is surgical removal of the diverticulum. Electrocoagulation of the duct and sac is not advised. Suprapubic drainage is uncalled for except in instances of complication.

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<sup>52</sup> Schmitz, H. E., and Nelson, P. A. Suburethral Abscesses, Urine Pockets and Diverticula in the Female Urethra. *Am J Obst & Gynec* 38:707-711 (Oct) 1939.

*Resistance*—Langworthy, Drew and Vest<sup>53</sup> stated that the collapsed urethra offers a certain resistance to the escape of urine from the bladder. In addition, they recognized three more specialized sphincteric mechanisms which can be distinguished in the experimental animal. The vesical orifice is normally closed and is pulled open by the contraction of the detrusor muscle and by the increased intravesical pressure. Sympathetic nerve fibers innervate muscle in the region of the verumontanum, this muscle has a sexual function and is particularly well developed in the male. Finally, the external sphincter and the perineal muscles form a voluntary sphincter. Section of the pudendal nerves, the sacral nerve roots and the sympathetic nerve fibers did not alter materially the urethral resistance. Abnormalities of micturition referable to injury of the nervous system are dependent primarily on difficulties of contraction of the detrusor muscle and only secondarily on changes in urethral resistance. The term "sphincter disturbances" is a misnomer.

#### TESTICLE

*Tumors*—Shane<sup>54</sup> reported a case of tumor of the testis in an infant. The child was 4 months old. Two weeks after birth of the child the mother first noticed an enlargement of the left testicle. Both testicles were descended, the right testicle was normal in size, but the left had enlarged to the size of a small hen's egg. The testicle was removed at operation, and on examination the tumor was found to be well circumscribed and not extended beyond the limiting capsule. Microscopic examination showed the tissue to be primary embryonal carcinoma, grade 2. Five months later the patient was in good health, with no evidence of recurrence.

Cabot and Berkson<sup>55</sup> gave survival rates concerning 73 patients treated at the Mayo Clinic for testicular tumor and known massive metastasis. Forty-seven patients received irradiation alone, 26 underwent orchidectomy followed by irradiation (13 had carcinoma, 13 had seminoma). Of the 47 patients, a group for whom the outlook appeared particularly unfavorable, only 17 per cent survived at the end of three years, and only 11.6 per cent were living at five years. Some patients lived as long as nine, thirteen and sixteen years. Of the cases in which orchidectomy was followed by irradiation, with known massive metastases, 38.5 per cent of the patients were alive at the end of three years,

<sup>53</sup> Langworthy, O. R., Drew, J. E., and Vest, S. A. Urethral Resistance in Relation to Vesical Activity, *J. Urol.* **43** 123-141 (Jan.) 1940.

<sup>54</sup> Shane, J. H. Tumor of the Testis in an Infant. *J. Urol.* **42** 236-239 (Aug.) 1939.

<sup>55</sup> Cabot, H., and Berkson, J. The Outlook for Patients with Malignant Tumors of the Testis Associated with Massive Metastasis, *Proc. Staff Meet. Mayo Clin.* **14** 377-380 (June 14) 1939.



32 per cent were alive at the end of five years, and 26.7 per cent were alive at the end of ten years. Of these, for the patients who had carcinoma the five year survival rate was only 15.4 per cent, for those who had seminoma it was 50 per cent. Analyses of all cases in which the patients survived three years or more are given in two tables.

Chevassu and Carrillon<sup>56</sup> drew attention to cancers of the testicle which developed on testicles that had been ectopic and that had been brought down surgically. Chevassu has had only 2 patients suffering from this condition among 350 patients who had tumors of the testicle and who came to consult him, Carrillon contributed reports on 3 more, from the urologic service at the Val-de-Grâce hospital. In Carrillon's cases the histologic diagnoses were epithelioma developing from wolffian rests, neoplasm of the wolffian type suggesting a cancerous dysembryoma, and dysembryoma of the wolffian type in a state of degeneration. Chevassu took some exception to a diagnosis of wolffian epithelioma, writing that he has not seen any cancers of the testicle that could be ascribed frankly to this origin.

In Chevassu's first case, in which the patient was a man aged 42, the lesion was proved histologically to be a seminoma. The cancerous testicle had been brought down from its ectopic position sixteen years previously and had remained in good condition until one year prior to Chevassu's observation. Operation and roentgen therapy reduced the tumor from the size of a fist to that of a bean, after which it refused to shrink further. A second series of treatments had no effect. The cancer metastasized, and the patient is known to have died in the following year. This experience caused Chevassu to protest against simple radiation therapy. In his second case he treated the patient by surgical removal of the lesion followed by two series of roentgen treatment and has achieved a three year cure, with this patient in excellent condition at the time of writing.

In the French literature there are only 14 cases on record of ectopic testicle in which cancer developed. These were the cases of Chauvin, Fey and the present authors. Five of the testicles were brought down in childhood, when the patients were 8, 9, 11, 13 and 13 years old respectively. The cancers that developed were treated surgically when the patients were respectively 30, 36, 20 and 23 years old. In other words the interval was long—between seven and twenty-three years. In 7 cases the testicle was brought down when the patients were 15, 20, 20, 26, 26, 27 and 32 years old, and the carcinoma was removed when the patients were 15, 25, 35, 26, 42, 43 and 33 years old respectively.

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<sup>56</sup> Chevassu, M., and Carrillon, R. Cancers testiculaires developpes sur les testicules ectopiques apres leur abaissement operatoire, *J. d'urolog.* **47** 59-70 (Jan.) 1939.

Thus, in 3 of these cases the interval was very short, but in 3 it was sixteen years

It is evident that 14 cases represent an exceedingly small fraction of the cases of ectopic testicles that have been brought down into the scrotum. The question then arises: Must one conclude that testicles brought down are less likely to become afflicted by cancer than those that are left undescended? The frequency of carcinomatous degeneration of ectopic testicles must not be exaggerated. In Chevassu's series of 350 cases of cancer of the testicle, the number of ectopic testicles is only a few units. If such testes are predisposed to cancer, there is no proof of it, and such a predisposition does not appear to exist.

Chevassu expressed the tentative opinion that trauma facilitates the development of cancer of the testes. What role does ectopia play in trauma? Does orchidopexy represent a trauma? The 3 cases of Chauvin in which this operation was followed by carcinoma a few months later suggest that operation for ectopia may be more dangerous than ectopia itself.

It is difficult to know what advice to give in cases of ectopia. Possibly the urologist has the right to urge on the parents of children realization of the frequency with which an ectopic testis may become cancerous, but it seems doubtful that he has the right to urge on adults the sacrifice of a testicle on the ground that it may have a predisposition to cancer. The medical literature contains only 6 cases in which ectopic testicles brought down in adults became malignant. It seems probable that the urologist should explain to the patient (or to the parent, if the patient is a child), that this testicle is, at any rate, fragile and that it needs watching. After it has been brought down the patient should be kept under observation and examined from time to time to see if any change is occurring in the organ. Too many instances of cancer of the testicle are encountered by the surgeon too late because the patients have not been warned of the dangers of changes in size or consistency of the organ. The patient whose ectopic testicle has been operated on especially should be under observation. It must be said, however, that the number of cases in which cancer has developed in such testicles is at present too small for any valid conclusion to be reached.

Hunt and Budd<sup>57</sup> reported an instance of gynecomastia associated with interstitial cell tumor of the testicle. The patient was a man aged 42. He complained of enlarged, painful breasts and impotence. Both breasts were approximately equally hypertrophied, and a definite mass of mammary tissue could be outlined in each. The breasts were tender to pressure, but no tumor or nodule was palpable. The testicles

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57 Hunt, V. C. and Budd, J. W. Gynecomastia Associated with Interstitial Cell Tumor of the Testicle. *J. Urol.* 42: 1242-1250 (Dec.) 1939.

were of approximately the same size and were uniform in outline, but there was a slight difference in their consistency. On careful palpation of the right testicle a slight difference in the consistency between the upper and the lower pole was noticed suggesting the existence of a tumor of about 2 cm in diameter within the substance of the upper pole of the testicle.

A positive reaction to the Zondek test equivalent to "1,000 units of luteinizing hormone per liter of urine" was obtained by Dr. Mona E. Bettin. A diagnosis of tumor of the right testicle was made, and surgical exploration of the testicle was advised.

Through a right inguinal incision the right testicle was found to be normal in size and contour, but the slight difference in consistency between the upper and the lower pole was sufficiently definite to warrant incision of the testicle for confirmation. Immediately after exposure of the tumor, the testicle was removed, together with all the structures of the cord as high as the level of the internal inguinal ring.

The patient had an uneventful convalescence and was dismissed from the hospital on the fifth postoperative day. There was return of libido immediately after the operation, and within a month there was a definite reduction in the size of the breasts, somewhat less in the right breast than in the left. The patient was seen at frequent intervals and three months later the left breast had receded almost to its normal size, some prominence of the right breast persisting.

The testis was of normal contour and average size, measuring 5 by 3.5 by 3 cm. An incision in the upper pole had exposed an encapsulated tumor 2 by 2 by 2.5 cm, deep in the testicular substance. As the tumor was enucleated from the testicle, it appeared to be attached to the upper part of the corpus of Highmore by a fibrous pedicle. The surrounding testicular parenchyma was compressed and pale yellow. No change was noted in the cord or in the epididymis. The capsule of the tumor was a smooth, thin, transparent membrane containing numerous dilated blood vessels.

The diagnosis was interstitial cell tumor of the testis.

*Orchiopexy*.—Young<sup>58</sup> stated that he studied 8,000 cases of pulmonary tuberculosis as recorded in four great sanatoriums in Colorado. The records showed that the disease was arrested in about 67 per cent of the cases. If no genitourinary tuberculosis was present, the disease in about 72 per cent was arrested. Many of the patients went home apparently cured. Of those who had tuberculosis of the urogenital tract, a large percentage died. In fact, the largest percentage of deaths in tuberculosis sanatoriums, judging by the cases studied in Colorado,

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<sup>58</sup> Young, H. in discussion on Sargent, I. C. *Orchiopexy*. *J. Urol.* **42**: 860-862 (Nov.) 1939.

occurs among those patients who have the misfortune to have the genito-urinary tract involved by the process

Young expressed regret that in recent years several writers have taught that radical operation is not necessary for early renal tuberculosis. He said that they have propounded the very dangerous doctrine "If you get a very early case of tuberculosis of the kidney, don't operate. Sometimes these patients get well without operation." Young cited a case to show the fallacy of any such advice.

A patient who was wealthy, who was a sportsman with plenty of time and money and who could do whatever he wished came to Young suffering from extremely early tuberculosis of the left kidney. Young told the patient that he thought the kidney should be removed. That was a number of years ago, and injections of tuberculin were used considerably at that time. The patient had heard about this and said, "I live in Colorado. I can go to the best sanatoria or the best mountain resorts there, I can get the greatest experts to give me these injections of tuberculin." Young said he did not believe in this method, but the patient insisted that he wanted such treatment. He went to one of the greatest tuberculosis experts in the country. He received a full series of injections. Three years later he was brought back into the hospital on a stretcher and died in about two weeks. Necropsy was done. The left kidney was completely destroyed, the other kidney was involved, as were both seminal vesicles, both lobes of the prostate gland and both epididymides.

As to whether the epididymis, the seminal vesicle or the prostate gland is the initial focus, it does not make much difference. Certainly the seminal vesicles or the prostate gland show involvement in a very large percentage of cases. Young stated that he had a rude awakening a number of years ago, when he went over the cases in which he had treated patients by castration and later by epididymectomy. On very careful study of 175 cases he found that a large percentage of the patients were dead. They had died of tuberculosis of the prostate gland, seminal vesicles, kidney and lungs. That rude awakening caused him to investigate the problem of some form of treatment for tuberculosis of the deeper portion of the genital tract, and since then, he stated whenever he has been able to show that tuberculosis of the seminal vesicles and the prostate gland, either or both, exists he has operated. Young gives the opinion of himself and his staff, because a great many of the operations have been done by his associates and also by the residents, who have become very proficient in it. Their opinion is unanimous that they have saved many a life by radical surgical intervention.

In 27 per cent of those cases in addition to taking out the entire seminal tract that is, the epididymides the vas the vesicles and the

lobes of the prostate gland, Young has also taken out one kidney, and in a number of cases in which such extensive operations were done the patients were well at the time of his report

#### EPIDIDYMIS

*Tuberculosis*—Ormond and Meyers<sup>59</sup> reviewed a series of 35 cases in which "genital tuberculosis" has been proved by removal of the epididymis. This condition in itself is not very serious. Epididymectomy in the majority of cases is a satisfactory procedure, and orchidectomy is rarely necessary. Epididymectomy is not an emergency operation, and postponement of it until suppuration and rupture take place seems to do little harm.

In all cases every effort should be made to find and to eliminate, if possible, other forms of tuberculosis. Since tuberculous epididymitis is a symptom of more deeply seated tuberculosis elsewhere, the patient should whenever possible be treated like any other tuberculous subject, by means of rest, diet and care in a sanatorium.

The presence of Myco tuberculosis in the urine practically always indicates renal tuberculosis.

The epididymis may be the primary site of infection in the genital tract.

In Ormond and Meyers' series, clinical tuberculosis of the urinary tract, although the most common concomitant infection, was not invariably present. Its incidence was a little more than 50 per cent. When clinical renal tuberculosis is present it is probable that the genital tract is infected from the urine through the prostate gland.

Prostatic massage does not seem to make much difference in cases of genital tuberculosis but is to be avoided.

Thomas,<sup>60</sup> in discussing Ormond and Meyers' paper, stated that during the seven years prior to the time of his discussion he had observed 97 patients who had some of the lesions of tuberculosis of the genitalia. Eighty-seven per cent of this group had tuberculosis situated elsewhere, and of this number 78 per cent had pulmonary tuberculosis. He stated the belief that tuberculosis of the genital tract is usually secondary to renal tuberculosis and that the primary urogenital infection spreads from the kidney downward.

In the 63 cases of tuberculosis of the genitalia that were adequately studied 92 per cent of the patients had renal tuberculosis. Twenty-three patients suffering from genital tuberculosis came to necropsy, death being caused by pulmonary lesions, uremia and the like, all 23 patients

<sup>59</sup> Ormond, J. K. and Meyers, K. L. Tuberculous Epididymitis, *J. Urol* 42: 829-842 (Nov.) 1939.

<sup>60</sup> Thomas, G. I. in discussion on Ormond and Meyers<sup>59</sup> p. 857.

of this group had definite renal tuberculosis. In view of these statistics, Thomas stated the belief that tuberculosis of the genital tract is more often associated with and secondary to lesions of tuberculosis in the kidney.

His evidence is not 100 per cent conclusive, however, he stated that these data suggest that the descending mode of invasion of the genital tract is most frequently via the urine. In his clinical experience the epididymis seems to be more frequently involved than the prostate gland, although data obtained from necropsies reveal that 22 of the 23 patients had tuberculosis of the prostate gland, while only 14 of the 23 had tuberculosis of the epididymis. In other words the prostate gland is involved more often than are other genital organs.

Thomas showed a chart of data concerning the situation of the lesions in 200 cases of tuberculosis of the urogenital system. In 45 cases the lesions were situated in the prostate gland, in 40 in the bladder, in 16 in the epididymis, in 14 in the seminal vesicle, in 23 in the testes and in 13 in the epididymis and prostate gland. There were 3 cases of epididymal tuberculosis and 4 of tuberculosis of the seminal vesicle in which there was no gross evidence of prostatic tuberculosis. These were all gross observations. The kidney and prostate gland were not serially sectioned.

#### URINARY CALCULI

Chute<sup>61</sup> stated that urea-splitting bacteria are frequently found in association with and as the apparent cause of the formation of urinary calculi, especially recurrent and multiple calculi.

A review of all the cases of urinary stone in which the patients entered the Massachusetts General Hospital during 1937 showed that more than half had an infection with a urea-splitting organism as the only apparent cause. The commonest organism (60 per cent) was *Bacillus proteus*, next were nonhemolytic streptococci, staphylococci, *Bacillus pyocyaneus*, *Bacillus influenzae* and *Micrococcus flavus* in that order of frequency.

In 80 per cent of cases of recurrent stone the patients were infected with urea-splitting bacteria, and in 60 per cent of cases of infection with urea-splitting bacteria the patients had multiple or recurrent stones. Thus recurrent or multiple stones and such infections go hand in hand.

These infections, especially those caused by *B. proteus* are often difficult to cure. They are almost never eradicated permanently until existing stones and also stasis have been removed. Chronicity of infection lessens the chance of permanent cure. The use of ammonium chloride as a urinary acidifier for infections of this type is contraindicated. Sulfanilamide has been the most effective drug.

61 Chute, R. The Significance of Urea-Splitting Bacteria in the Formation of Urinary Calculi. *New England J. Med.* **219** 1030-1032 (Dec. 29) 1938.

## HYPERTENSION

Mulholland <sup>62</sup> stated that there is a definite entity, involving the renal circulation at the renal artery, or else an inflammatory entity within the kidney itself, that produces an elevation of the blood vessel tone. This pathologic process can be determined and, if diagnosed, removed, with cure of the hypertension, as has been proved in experimental work and in clinical cases. Hypertension should be considered in the same light as a fever, it is a symptom rather than a disease. Every patient who has high blood pressure should be given treatment especially planned for him, that means that this treatment may be inadequate and ill advised unless the physician knows the status of the kidney. Mulholland stated the belief that urologists can cure an increasing number of patients with hypertension. Experimental work and clinical cases may explain the failure of many of the operations done on the nervous system for the relief of hypertension. Perhaps after performance of "lumbar sympathectomy" there are relief of the vascular spasm in the renal vessels and a temporary improvement in renal circulation. However, because of the vascular changes that have occurred there is a return to the condition present before operation, the blood pressure is similarly affected. Certainly, before any patient suffering from hypertension is subjected to any of the operative procedures now in favor for the relief of hypertension, the kidney should be ruled out as the possible cause of the hypertension. Surely, with all the evidence suggesting that the kidney may be the primary factor in initiating hypertension, the structure demands the careful and thoughtful attention of every urologist. It is a real challenge to the urologist to identify pyelonephritis in the stage in which pallor, underweight and slight albuminuria are the only signs. It is only by means of searching inquiry with the foregoing facts in mind that urologists will be adding more and more cases to the literature and also more patients who might otherwise have been doomed to a hypertensive end to the list of those in whom satisfactory results were obtained.

Crabtree and Prien <sup>63</sup> noted that there was evidence of damage to the arterial blood supply in most portions of a kidney in a case of severe bilateral postpartum pyelonephritis in which one kidney had been removed at the height of the infection and in which the other kidney apparently had recovered. Since these vessels are terminal, the injury from the initial infection should be expected to produce irreparable cortical damage in such kidneys.

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62 Mulholland S W. Hypertension's Challenge to Urology, *J Urol* 42 957-968 (Dec) 1939

63 Crabtree, E G and Prien E L. The Nature of Renal Injury in Acute and Chronic Colon Bacillus Pyelonephritis in Relation to Hypertension. A Combined Clinical and Pathological Study, *J Urol* 42 982-995 (Dec) 1939

Clinical observation of 30 patients suffering from severe bilateral pyelonephritis during pregnancy from ten to eighteen years after the initial injury (the infection) showed that only 2 of these patients showed evidence of hypertension. When studies of renal function were made in the cases of 7 of these patients, all 7 exhibited severe degrees of renal injury.

Hypertension is not the rule in cases of severe injury to the kidneys referable to pyelonephritis occurring in pregnancy even remotely after the initial injury in patients who show reasonable degrees of health. This does not indicate whether these same patients may not be hypertensive nearer the end of life.

#### SURGICAL TREATMENT OF BLADDER, KIDNEY AND URETERS

Priestley<sup>64</sup> stated that during 1938 858 operations (exclusive of all transurethral procedures) were performed on 786 patients for various diseases of the genitourinary tract. There were 19 deaths in the hospital in the entire group of 786 patients, a mortality of 2.4 per cent.

During the three years prior to Priestley's report, the number of patients operated on for lesions of the kidney had increased steadily, and during 1938 there were 307 such patients. Approximately half (151) of these patients were operated on because of nephrolithiasis. Two deaths occurred in this group of 151 cases, a mortality of 1.3 per cent.

During 1938, 22 patients with stag-horn renal calculi were operated on, without mortality. In 18 cases the stones were unilateral, and nephrectomy was performed in 9 of these. In the remaining 9 cases a conservative operation was carried out, the stones being removed and the kidney preserved. In 4 cases bilateral stag-horn calculi were present, and bilateral conservative operations were performed in two stages. In no instance was secondary nephrectomy necessary.

The more widespread use of nephrostomy in selected cases has been of definite value. Nephrostomy not only permits the preservation of many severely damaged kidneys which otherwise might have had to be removed but reduces definitely the necessity for performance of emergency nephrectomy after various types of conservative operations on the kidney. During the past year nephrostomy was performed in approximately 30 per cent of the cases in which stones were removed from the kidney and in all cases in which nephrolithotomy was performed.

In 75 per cent of the 151 cases of nephrolithiasis in which the patients were operated on at the Mayo Clinic during 1938 conservative

<sup>64</sup> Priestley, J. T. Report of Urologic Surgery for 1938. *Proc. Staff Meet. Mayo Clin.* 15: 29-32 (Jan. 10) 1940.



operation was performed, that is, stones were removed and the kidney was preserved, and in only 25 per cent of cases was nephrectomy performed

Fifty-two patients were operated on for hydronephrosis during 1938. On 31 (59.6 per cent) of these nephrectomy was performed and on 21 (40.4 per cent) a conservative operation was performed. There were no deaths in this series, and secondary nephrectomy was not necessary in any case after conservative operation.

Nephrectomy was performed for renal tumors in 50 cases, with 2 deaths, and for renal tuberculosis in 20 cases, with 1 death. In 34 additional cases operations were performed for miscellaneous lesions of the kidney, with 1 death. A total of 307 patients underwent operations on the kidney during 1938, with 6 deaths, a mortality of about 2 per cent.

During 1938 ureterosigmoidostomy was performed in 13 cases, with 2 deaths. In 8 of these cases transplantation was performed as the preliminary stage to total cystectomy for carcinoma of the bladder. In this group of 8 cases the 2 deaths occurred.

Gradually, during recent years, as experience and efficiency with transurethral surgical procedures have increased, fewer and fewer suprapubic operations have been performed on the bladder. The first change in this regard was, of course, the introduction of transurethral prostatic resection. The added skill acquired by the urologist in carrying out this surgical procedure has enabled him to treat certain vesical lesions with equally satisfactory results. As a result, suprapubic operations on the bladder do not seem to be necessary as frequently as they were formerly. During 1938 the suprapubic approach was employed in the treatment of vesical neoplasm in 24 cases. Segmental resection for carcinoma of the bladder was carried out in 7 cases, without a death. Total cystectomy with preliminary transplantation of the ureters to the sigmoid was performed in 6 cases, with 1 death.

Operation was performed in 30 cases for cryptorchidism, the Meyer-Torek type of procedure being utilized most often. Results continue to be satisfactory after this operation for undescended testis. Operation was performed for hypospadias in 31 cases during 1938. The McIndoe operation, which has for its principle the use of an inlying tubular graft, has been giving increasingly satisfactory results in the surgical treatment of this condition.

#### TRANSURETHRAL OPERATIONS

Thompson<sup>65</sup> stated that a total of 4,073 patients were subjected to 7,656 transurethral operations in 1937 and 1938 at the Mayo Clinic. Since it is necessary in some instances to perform transurethral prostatic

<sup>65</sup> Thompson G. J. Transurethral Surgery in 1937 and 1938. *Proc. Staff Meet. Mayo Clin.* **14**: 657-661 (Oct. 18) 1939.

resection in more than one stage, 1,791 operative procedures were performed on 1,697 patients. Sixteen hundred and seven of these patients were operated on in one stage, 86 in two stages and 4 in three stages. Thus, in 94.7 per cent of cases transurethral resection in one stage sufficed. That transurethral resection has replaced other types of prostatectomy is evident from the fact that in only 2 cases was suprapubic enucleation done for benign hypertrophy during this period of two years. In 1 other case prostatectomy was done for sarcoma. It was necessary to perform cystostomy preliminary to transurethral resection in only 5 cases.

In not a single case during the two years was suprapubic cystostomy performed for the treatment of advanced renal insufficiency or for severe infection of the urinary tract. Thompson and his co-workers were able by careful selection of methods, to carry on with drainage through a urethral catheter until transurethral resection was feasible. Success with this method of drainage hinges on vigilance and cleanliness in keeping open the proper type of urethral catheter, which has been carefully adjusted. It must be recognized, however, that some patients will not tolerate an indwelling catheter and must be catheterized carefully at regular intervals until operation can be performed.

The mean average age of the patients during the two years was 66.2 years. There were 71 patients aged 80 years or more, and of these only 1 died, which seems to prove the relative safety of transurethral resection in comparison to other forms of prostatectomy.

The amount of tissue resected in the average case is interesting. If the small-bar type of prostate gland and contracted vesical neck are eliminated from consideration, it is found that the average amount removed during 1938 was 32.1 Gm. in each case.

In the large majority of cases less than one week of postoperative hospitalization was required, and of equal importance is the fact that only 25 patients of the total of 1,697 were in the hospital more than three weeks, of these, only 7 spent more than one month in the hospital after operation.

The mortality following transurethral prostatic resection during the two years was 1.6 per cent (27 deaths among the 1,697 patients).

Thompson's charts show that stones were removed from the ureter in 140 cases, a total of 199 manipulations being required. In the large majority of cases the stone was removed at the first attempt being extracted from the ureter as a rule while the patient was on the cystoscopic table. There is no procedure in transurethral surgery which requires so much patience as the manipulation of a ureteral calculus.

After extracting a ureteral stone, Thompson wrote, he always places a ureteral catheter in the ureter and a urethral catheter in the bladder, so that for forty-eight hours all drainage of urine is mechanical, and the edematous ureter and trigon have time to recover from the trauma of manipulation

Litholapaxy was performed in 142 cases. This, too, is a procedure which saves the patient many days in the hospital. During these two years, suprapubic lithotomy was performed only 11 times, this indicates that most vesical calculi can be removed without resorting to open operation

The destruction of tumors of the bladder by transurethral fulguration was carried out in 374 instances. This includes those cases in which treatment by either transurethral or open operation in previous years had been followed by recurrence. For a number of patients presenting large papillary growths of low grade malignancy, the bulk of the tumor was removed by means of a cystoscopic forceps or resectoscope. Radon seeds were implanted in small tumors of a high grade of malignancy in 28 cases

It is interesting that intravenous anesthesia was used in 1,882 cases. Since most of the procedures are of short duration, the intravenous injection of pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) by the fractional method is satisfactory. Thompson has found that transurethral prostatic resection can be performed in most cases in less than twenty minutes, and for patients aged 80 years or more who are in rather poor condition the intravenous method of producing anesthesia is far superior to other types, there is less bending and manipulation of the patient, he can sit up in bed a few hours after operation, and thus the chance of pulmonary and other complications is minimized. Spinal anesthesia was employed in 1,548 cases, with highly satisfactory results. Procaine hydrochloride injected through the fourth lumbar interspace in a dose of 80 mg or less, depending on the weight and age of the patient, provides anesthesia for approximately one hour for transurethral prostatic resection or other intravesical manipulation. It seldom causes serious reactions. Inhalation anesthesia with nitrogen monoxide is the method of choice for infants and children and was used in 72 cases. Sacral block anesthesia was employed only 37 times because in Thompson's opinion, severe physiologic reaction to the large amount of procaine hydrochloride which must be injected is observed frequently among men of an age at which prostatic disease is likely to occur. This chance for such a reaction to occur far outweighs any theoretic advantages which the method has over spinal anesthesia.

## BACTERIOLOGY OF URINARY TRACT INFECTION

Schulte<sup>66</sup> studied the bacteriologic aspects of the urinary tract in normal persons and patients by inoculating 0.5 cc of urine into dextrose-brain broth and hormone-blood agar pour plates. Subsequent identification of the organisms was made by using other mediums. For normal controls, only those persons were used who were not suffering from any clinical infection of the genitourinary tract and who, in addition, had negative smears in a Gram stain of the urinary sediment and prostatic secretion.

Schulte studied four groups of normal men. In the first, the second portion of the voided urine of a clean specimen was used. Small numbers of colonies of nine different organisms were found, of which micrococci, diphtheroids and *Streptococcus faecalis* were most common. The second group, in which the urine was obtained by catheter, gave similar results, with fewer colonies. The third group, in which the urine was obtained as in the first group but after lavage of the anterior portion of the urethra, was divided into two equal subgroups, one having sterile urine, the other urine infected by *Micrococcus*. After voiding, prostatic massage was done. Culture of the secretion showed alpha streptococci in practically all cases and in those with micrococci in the voided specimen micrococci as well. Schulte concluded that micrococci are normal inhabitants of the anterior portion of the urethra and alpha streptococci of the posterior part of the urethra and the prostatic secretion.

Schulte also studied a fourth group, for which retrograde pyelograms were made. Urine obtained from the bladder cystoscopically gave the same results as have been recounted, but the results of examination of the urine from the renal pelvis were consistently negative. From this Schulte concluded that cystoscopic examination introduces bacteria from the urethra into the bladder. Schulte pointed out that this method of bacteriologic study will reveal those instances of clinical infection missed by Gram-staining of urinary sediment or of prostatic secretion. *Staphylococcus aureus* was never isolated from the urine or the prostatic secretion of normal subjects.

Schulte described a medium in which an organism's urea-splitting ability may be tested, using thymol blue as an indicator and quantitative determinations for ammonia. On this medium, Schulte found *Proteus ammoniae* and *Micrococcus ureae* to be the worst offenders. *Str. faecalis* did not utilize urea at all. Occasionally other organisms would split urea as much as would the aforementioned two. By culturing on this medium

<sup>66</sup> Schulte T. L. Newer Methods in a Study of the Bacteriology of the Urinary Tract. Preliminary Report, Proc. Staff Meet. Mayo Clin. 14:249-254 (April 19) 1939.

first it is possible to prevent overgrowth of other organisms and thereby make isolation more complete

Schulte also checked the pathogenicity of gram-positive, mass-forming cocci in vivo on rabbits and guinea pigs and in vitro in human or horse serum. Correlation between the tests was 90 per cent. The coagulose test also differentiated the staphylococcus from the micrococcus.

Thompson and Schulte<sup>67</sup> described a medium on which the urea-splitting ability of an organism may be tested. The composition of the medium is peptone 0.2 per cent and sodium chloride 0.5 per cent in distilled water. To each liter 20 cc of 0.2 per cent alcoholic solution of thymol blue is added. The  $p_H$  is then 6.8. The solution is sterilized in amounts of 10 cc. A solution of 10 per cent urea, sterilized by filtration, is added to the sterile tubes until the concentration of urea is 0.5 per cent. When the  $p_H$  reaches 9.4, the medium is deep blue. A positive reaction to this test is one in which this color is obtained within forty-eight hours, an experimentally determined standard. The blue color occurs when the level of free ammonia is not less than 25 mg per hundred cubic centimeters. It was found best to use 0.5 cc of urine as the inoculum. Three hundred specimens were studied, 200 were range finding and 100 for more intense study. Of these 100 specimens 24 were positive, yielding *Proteus* (13), diphtheroids (7), micrococci (2) and *Salmonella morganii* (2). In some cases the urea-splitting organism was detected only in this medium, and was not found when blood agar or eosin-methylene blue mediums were employed. Thompson and Schulte emphasized the importance of studying the urine for urea-splitting organisms in instances of (1) persistently alkaline urine, (2) acute diffuse fulminating hemorrhagic cystitis, (3) incrustations and (4) urinary calculi. Cases of acid urine and oxalate and urate stones were not involved, but in those cases in which alkaline urine and phosphate or carbonate calculi were present, more than 50 per cent had a urea-splitting organism present. Thompson and Schulte discussed some of the aspects of urea-splitting organisms which are of clinical importance. The present study constitutes a preliminary report. The importance of adding a few drops of urine to the urea broth is emphasized.

Crenshaw and Cook<sup>68</sup> pointed out the value of sulfanilamide in treating bacillurias (*Escherichia coli*, *Aerobacter aerogenes*, *Salmonella*, *Proteus*) of all sorts, especially those complicated by obstruction or chronic prostatitis. Mandelic acid therapy is still the best for use in cases of uncomplicated bacilluria. Neither sulfanilamide nor mandelic

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67 Thompson, L., and Schulte, T. L. Urea-Splitting Organisms in Urine. Preliminary Report, Proc. Staff Meet., Mayo Clin. **14** 361-364 (June 7) 1939.

68 Crenshaw, J. L., and Cook, E. N. Limitations, Dangers, and Failures of Sulfanilamide in the Treatment of Urinary Tract Infections, J. Urol. **41** 64-68 (Jan.) 1939.

acid is of much value in cases of nonspecific prostatitis. It is the best drug for a *Proteus* infection, but it is relatively inefficient in eradicating *Str. faecalis* and staphylococci. The micrococci fall into a variable intermediate group.

Crenshaw and Cook pointed out that dangers may be avoided by close supervision. Ten per cent of patients cannot take sulfanilamide. A high percentage have toxic symptoms of which headache, malaise and weakness are the most common. Fever and cyanosis are indications for discontinuing the drug. Cyanosis portends methemoglobinemia or sulfhemoglobinemia as well as acute hemolytic anemia and granulocytopenia. Cutaneous reactions are of two types, increased sensitivity to light and a morbilliform rash. Two thousand patients suffering from urologic conditions received the drug, with only 3 severe reactions.

The dose was in most cases 40 grains (2.6 Gm.) daily for patients who had nongonorrheal conditions. In instances of gonorrhea, doses of 60 grains (4 Gm.) given daily for three or four days are followed by doses of 40 grains daily for seven days. In order to prevent a decrease in the carbon dioxide-combining power of the blood caused by sulfanilamide, Crenshaw and Cook advised administration of magnesium oxide, 1 or 2 grains (0.065 or 0.13 Gm.) with each tablet of the drug. The use of saline cathartics is forbidden. When sulfanilamide therapy or fever therapy alone fails in eradicating the gonococci, the two may succeed when combined. The para form of the drug is the most effective.

Thompson<sup>69</sup> pointed out the unsatisfactory management of patients who have an obstructing enlarged prostate gland in the presence of chronic renal insufficiency prior to the introduction of transurethral surgical procedures. The treatment of patients with such a condition was prolonged and disappointing, and it occasionally ended without surgical treatment other than permanent suprapubic drainage. With careful preoperative and postoperative care, such patients now achieve complete relief quickly by means of transurethral resection. Thompson's illustrative case was one in which a man 52 years of age had had symptoms of prostatic obstruction for two years and loss of strength, drowsiness and vomiting for two months. On admission he was dehydrated, anemic and underweight (loss of 40 pounds, or 18 Kg.) and had mild convulsions and Kussmaul's breathing. The bladder extended to the umbilicus. The prostate gland was only moderately enlarged on rectal examination. Treatment consisted of installation of an indwelling urethral catheter and parenteral administration of fluids (5 per cent dextrose in physiologic solution of sodium chloride, lactate-Ringer [Hartmann's] solution

69 Thompson, G. J. Transurethral Resection in the Presence of Marked Renal Insufficiency. Report of Case. *Proc. Staff Meet. Mayo Clin.* **14**: 401-404 (June 28) 1939.

and 5 per cent solution of sodium bicarbonate) daily. By means of this treatment the value for urea in the blood, which on admission had been 488 mg per hundred cubic centimeters, was reduced to 124 mg on the day of operation, twenty-three days after admission. The carbon dioxide-combining power had been 12.6 volumes per cent on admission, and this was satisfactorily controlled. With intravenous anesthesia produced by pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) 19 Gm of prostatic tissue was removed by transurethral resection. Convalescence was uneventful. Postoperative examination showed no residual urine, there had been 650 cc on the patient's admission. The value for blood urea when a determination was last made was 104 mg per hundred cubic centimeters. The patient's symptoms and general health had improved markedly at the time of Thompson's writing. Patients previously and similarly treated have, as a group, shown improvement in their general health.

Sandholzer and Scott<sup>70</sup> presented the results of a study of the aerobic gram-negative bacilli encountered in infections of the genitourinary tract. In all, 530 cultures of material from 283 patients were subjected to detailed investigation with the aim of ascertaining whether any relation between the type of organism present and the response of the patient to treatment could be discovered.

The bacteria consisted of six genera. Members of *Escherichia* were found in 83 per cent of the cultures (27 species or types) and members of *Aerobacter* in 13 per cent (14 species or types), whereas the remaining 4 per cent were distributed among the genera *Salmonella*, *Proteus*, *Shigella* and *Pseudomonas*.

Hemolytic activity was determined on rabbit's blood-pork infusion agar in pour plates. Although all of Brown's types of hemolysis were observed, the type was independent of the genus or species of the organisms present.

When specimens of urine from the same subjects were cultured at intervals over a period of months, the type of organism recovered in some instances remained constant as to species and type of hemolysis but in other instances variations in either one or both of these factors occurred. Thus, from 1 patient nine different species belonging to three genera were recovered at various times.

Correlation of the bacteriologic observations with the clinical records suggests that differences in the therapeutic response of patients who have bacillary infections of the urogenital tract may depend to some degree on the particular type of gram-negative bacillus responsible for the infection.

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70 Sandholzer, L. A., and Scott, W. W. A Bacteriological and Clinical Study of Bacillary Infections of the Urogenital Tract, *J Urol* 42: 183-196 (Aug.) 1939.

## HERNIA AND INFECTION OF THE URINARY TRACT

Seaman<sup>71</sup> stated that the predisposing cause of hernia is the persistence of the vaginal process, which accompanies the testicle in its descent into the scrotum. It rarely causes pain, even when it exists.

Pain in the groin and epididymis referable to prostatovesiculitis frequently is mistaken for evidence of hernia.

Performance of herniorrhaphy for pain alone is never justifiable.

Infection in the lower portion of the urogenital tract is often hidden.

The "injection" method of treating patients who have pain but no hernia should not be condoned.

Pain following herniorrhaphy is frequently the result of vasitis and not of nerves being caught in the line of sutures.

Mandelic acid and sulfanilamide are two great adjuvants in the treatment of prostatovesiculitis.

Leukorrhea has not been stressed sufficiently as a cause of prostatovesiculitis.

Cases involving the aforementioned conditions will not be adequately adjudicated in the courtroom until the diagnosis in all instances has been made properly.

## UROGRAPHY

Crane<sup>72</sup> reported a case in which sudden death occurred following intravenous administration of diodrast (3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine). Thirty cubic centimeters was injected in the usual manner during about two minutes. After this, the patient became cyanotic, and his respirations decreased to 6 per minute. Death occurred about twenty minutes later in spite of the use of the usual restoratives. The cause of death as indicated by necropsy was edema of the lungs and of the larynx. A small number of cases of this type have been reported in the literature. In most of them, as in Crane's case, the patients were very ill.

Wesson,<sup>73</sup> in discussing the case reported by Crane in which death followed the intravenous administration of diodrast for intravenous urographic study, cited the work of Robb and Steinberg, who used large amounts of the medium injected very rapidly for the purpose of showing the outline of the heart. These investigators have used this technic in 456 cases, without the occurrence of a single death.

In a discussion of urography, Braasch<sup>74</sup> stated that at the Mayo Clinic excretory urographic methods have been employed for approximately 25,000 patients, without occurrence of a death.

71 Seaman, J. A. Hernia and Lower Urological Tract Infection. *J. Urol.* **42**: 887-892 (Nov.) 1939.

72 Crane, J. J. Sudden Death Following Intravenous Administration of Diodrast for Intravenous Urography, *J. Urol.* **42**: 745-748 (Nov.) 1939.

73 Wesson, M. B., in discussion on Crane,<sup>72</sup> p. 754.

74 Braasch, W. F., in discussion on Crane,<sup>72</sup> p. 757.



Nesbit and Douglas<sup>75</sup> stated that the subcutaneous administration of adult doses of diodrast in proper dilution with physiologic solution of sodium chloride is entirely safe and technically advantageous. No ill effects, either local or systemic, were noted in any of their cases.

The solution is absorbed completely in forty-five to sixty minutes. Optimal excretion of the dye in the normal kidney occurs in ten to thirty minutes after injection.

This method has an advantage over intravenous pyelographic methods for infants in its ease of administration as well as in the higher incidence of diagnostic roentgenograms thereby obtained.

Schulte and Emmett<sup>76</sup> reviewed urographic studies made in 112 cases of retroperitoneal extrarenal tumor, proved at operation, hoping to find some diagnostic characteristics in the urograms. The 112 cases may be divided into two groups: (1) 40 cases in which the retroperitoneal tumor did not originate in the pancreas or kidney and (2) 72 cases in which the tumor originated in the pancreas. In 29 (72.5 per cent) of the first group of cases, examination of the urograms disclosed displacement of the kidney or the ureter or both. In these cases the displacement was very evident, the kidney and ureter most often were definitely displaced medially or laterally. In a few cases, however, the kidney was displaced upward or downward, and there occasionally was evidence of bizarre types of renal rotation in various planes. In 68 (94.4 per cent) of the 72 cases in group 2 there was no displacement of the kidney or ureter. Histopathologic examination revealed that most of the tumors in the cases of group 1 were sarcomas, whereas in the cases in group 2 approximately two thirds of the tumors were adenocarcinomas, and a third were cysts.

#### TESTOSTERONE PROPIONATE

McCullagh and McGurl<sup>77</sup> stated that complete sexual maturity can be developed in instances of severe testicular deficiency by injection of testosterone propionate. The attainment of normality in some features, such as beard and prostatic growth, requires larger doses and a considerably longer time than is required for the response of other structures.

Testicular descent has occurred in 3 of 10 cases, and the testes have increased in size, as judged by palpation, in 2 cases. Skeletal maturation

<sup>75</sup> Nesbit, R. M., and Douglas, D. B. The Subcutaneous Administration of Diodrast for Pyelograms in Infants, *J. Urol.* **42**: 709-712 (Nov.) 1939.

<sup>76</sup> Schulte, T. L., and Emmett, J. L. Urography in the Differential Diagnosis of Retroperitoneal Tumors, *J. Urol.* **42**: 215-219 (Aug.) 1939.

<sup>77</sup> McCullagh, E. P., and McGurl, F. J. Observations on the Clinical Use of Testosterone Propionate, *J. Urol.* **42**: 1265-1273 (Dec.) 1939.

in hypogonadal men receiving doses varying approximately from 75 to 150 mg per week may advance at a rate exceeding the normal

Injections of testosterone propionate cause a pubertal type of acne

A case is described in which repeated examinations of the semen showed the total production of sperm to decrease markedly during therapy. There was an apparent though less definite decrease in the motility of spermatozoa and in the volume of the semen

Results of testosterone propionate therapy in 4 cases of gynecomastia are reported, with comments on this therapy for 14 women, in 2 of whom treatment produced evidences of virilism

#### HEMATURIA

Barach and Pennock<sup>78</sup> stated that the orthotolidine test is a sensitive method of determination of occult hematuria. A positive reaction to this test was obtained in one third of 681 general cases of the so-called chronic diseases in which treatment was medical. Occult bleeding is less common in youth, when there are more intact vessels, and it is more common in females than in males, because of the greater source of bleeding in the female generative tract. Seasonal variation pointed to the highest incidence during the summer months. Albuminuria and occult blood are found independently of each other, each having its own significance. Glycosuria is not a cause of occult bleeding. Arsenicals in therapeutic doses do not cause occult bleeding. Alkalinity or acidity of the urine is not a cause of occult bleeding. In patients showing persistent occult hematuria, hypochromic anemia is common. A review of the type of case in which the strongest reactions occurred reveals that these reactions were most pronounced in the clinically recognized serious types of disease and that the test reflects the patient's actual condition.

#### ANURIA

Kutzmann<sup>79</sup> stated that anuria is a serious clinical condition and therefore is of great importance.

Anuria may be of either the prerenal or the renal secretory type or of the postrenal, or obstructive, type. With the former the causative factors are either proximal to or are in the kidney itself whereas with the latter the cause lies in or distal to the renal pelvis.

<sup>78</sup> Barach J H, and Pennock L L. Diagnostic Value of Occult Hematuria. A Study of Three Thousand Specimens of Urinary Sediment. *J A M A* **114** 640-642 (Feb 24) 1940

<sup>79</sup> Kutzmann A A. Anuria. A Clinical Study. *J Urol* **42** 1274-1299 (Dec.) 1939

There are many etiologic factors in anuria, but they may conveniently be grouped into (1) prerenal, (2) renal, (3) postrenal—intrinsic and extrinsic—and (4) a transitional or combination group

Clinically, a patient who has anuria may be considered as being in the period of tolerance when no signs or symptoms except the anuria are noted, as being in a period of minor intolerance when mild nausea, vomiting hiccup headache, and diarrhea are noted, and as being in a period of major intolerance when the given signs and symptoms progress to convulsions and coma and finally to death

The diagnosis of anuria is made from a carefully taken history, physical examination, absence of urinary secretion, plain roentgen study, ureteral catheterization and studies of the blood chemistry

Treatment consists of an immediate diagnosis as to the type of anuria, supportive treatment for the secretory type and immediate drainage either by ureteral catheterization or operation for the postrenal or obstructive type, supported by the usual administration of fluids. Surgical intervention may be indicated in any well selected case of anuria. The prognosis is much better for the obstructive type than for the secretory type of anuria

Five personal cases of anuria are presented (1) a case of nephritis in which there was anuria of eighteen days' duration and in which there was a level of 300 mg of nonprotein nitrogen and 24 mg of creatinine per hundred cubic centimeters of blood, (2) a case in which postrenal reflex anuria followed ureteral catheterization, (3) a case in which secretory anuria was caused by necrosis of the tubular epithelium following cholecystectomy and was associated with acute hemorrhagic pancreatitis, (4) a case in which postrenal or obstructive anuria was referable to a calculus situated in the ureter of a remaining kidney, and (5) a case in which postrenal and renal secretory anuria was associated with a value for nonprotein nitrogen of 267 mg and a value for creatinine of 40 mg per hundred cubic centimeters of blood, in this case the condition was caused by an extrinsic bilateral ureteral obstruction due to diffuse retroperitoneal carcinomatosis

#### RENAL DIGESTIVE REFLEX

Emerson, Smith and Orkin<sup>80</sup> stated that an analysis of 487 consecutive cases of disease of the upper part of the urinary tract showed that in 50 (10.2 per cent) a diagnosis of lesion of the digestive tract had been made and that the average duration of symptoms referable to the gastrointestinal and urogenital tracts was four years and one and nine-

<sup>80</sup> Smith, E., and Orkin, L. The Renal Digestive Reflex, *J Urol* 43 1-17 (Jan) 1940

tenths years respectively. There was no case in which the urogenital complaints preceded the gastrointestinal symptoms.

Twenty-three patients had undergone a previous abdominal operation, without benefit. In this group 20 had never had any urogenital symptoms prior to, and 10 never had any urogenital symptoms before or after, abdominal operation.

The authors demonstrated the reflex nervous mechanism by means of which a diseased kidney may cause symptoms in the digestive tract. This mechanism also explains the reason that a urinary lesion on one side may give rise to symptoms in the digestive tract on the other side, of which condition 6 cases are reported.

From a consideration of all observations, they suggested that for any patient who has undergone previous abdominal surgical exploration with no relief of symptoms or any patient in whose case the history and the results of physical and gastrointestinal laboratory examination do not dovetail urologic investigation should be done.

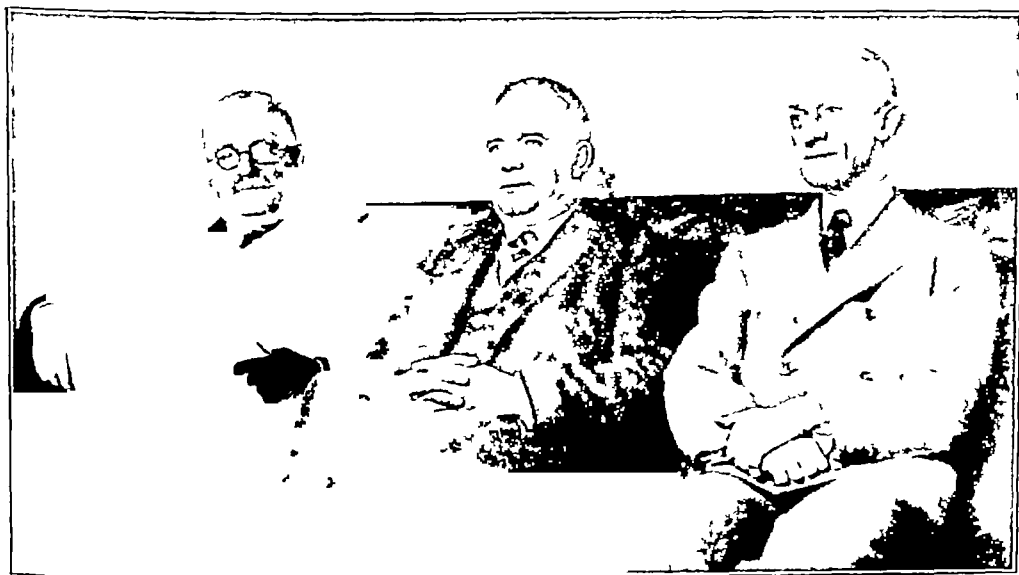
#### ANESTHETIC AGENTS

Tuohy and Thompson<sup>81</sup> recommended solutions of 2 per cent cocaine, 4 per cent metycaine or 1 per cent diothane (but not procaine) locally for simple procedures. When the surgeon is dealing with apprehensive or hypersensitive patients, the intravenous administration of pentothal sodium (sodium-1-methylbutyl-thiobarbituric acid) may be advisable. The advantages of this type of anesthesia are easy induction and a short recovery period and the noninflammable nature of the agent. It therefore has replaced anesthesia produced by inhalation anesthetic agents to a large degree, especially for elderly, hypertensive or debilitated patients and in procedures in which considerable electrical equipment is used. Rectal anesthesia (avertin with amylene hydrate) is used only occasionally, because of its depressing effect on the systolic blood pressure.

For transurethral prostatectomy, Tuohy and Thompson outlined a course of premedication. For the sturdier patients, low spinal anesthesia may be produced by a moderate dose. The importance of preventing vascular collapse by using the interspace of the fourth and fifth lumbar vertebrae is emphasized. Ephedrine sulfate (3/8 grain, or 0.024 Gm.) is used routinely in the production of local anesthesia at the site of the lumbar puncture except in cases of hypertension. If the pressure decreases subsequently, ephedrine sulfate administered intravenously helps to maintain the vascular tone.

<sup>81</sup> Tuohy, E. B. and Thompson, G. J. Methods of Anesthesia for Transurethral Prostatic Resection and Other Cystoscopic Procedures. *J. Urol.* **42**: 642-649 (Oct.) 1939.

For Tuohy and Thompson intravenous anesthesia was the method of choice in approximately 50 per cent of 3,480 procedures performed on the lower part of the genitourinary tract. Most of the remainder were done under spinal, block or local anesthesia. Tuohy and Thompson reported in some detail their method of producing anesthesia intravenously. Fractional administration of a 2.5 per cent solution of pentothal sodium is used. Ephedrine sulfate, oxygen and parenteral fluids are given on the operating table as indicated.



Dr J M T Finney, Dr Dean Lewis and Dr Harvey Cushing The photograph was taken by Dr J Murray Washburn, of Lake Lure, N C, on the occasion of the testimonial dinner given in Baltimore for Dr Lewis in 1926



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DEAN LEWIS

A BIOGRAPHIC SKETCH

VERNON C DAVID M.D.

CHICAGO

Appraisal and appreciation of real achievement in a man's life comes too often as an epitaph. It is pleasant, therefore, to make one of the noteworthy exceptions in this Dean Lewis birthday issue of the ARCHIVES OF SURGERY, which, by their contributions to it, affords a few of his associates and pupils an opportunity of indicating for his many friends their admiration of his achievements and their affection for him as a man and of wishing him many more years of active and happy life.

To attempt to paint the picture of Dean Lewis (for those who know him) is a footless effort. Individualism and friendly aggressiveness often stand out as impressions on meeting him for the first time. As a student in his class in surgical anatomy I was struck by his complete dominance of the scene, his accurate and historical knowledge of his subject and his alertness to the reactions of his class and subconsciously by the fact that anatomy in his exposition of it was no longer a dead but a bright, living subject. This is an indirect way of saying that nearly all men are instantly attracted to him and that his great influence on the development of his pupils and associates is a natural result of obvious forces.

After his graduation in 1895 from Lake Forest College and in 1899 from Rush Medical College, where he came under the influence of Billings, Herrick, Senn and Bevan, he interned at Cook County Hospital, an institution which has made a deep and lasting impression on the surgical consciousness of the Middle West. With him as intern colleagues in the hospital were Rowan, Wells, Kanavel, Besley and Richter, and dominating the scene as attending surgeons were Fenger, Murphy, Ochsner, Andrews and Harris. A recital of these names, so well known to American surgeons, indicates that inspiration for hard work and good fellowship abounded.

On completion of his internship he accepted a position as instructor of anatomy at the University of Chicago and for four years arduously devoted himself to his task, with a consequent sound knowledge of



anatomy which, coupled with an unusual memory for its details, has often subsequently brought amazement to his colleagues and consternation to his medical students. Coming under the influence of Bensley, then professor of anatomy, he became interested in vital staining of tissue and, utilizing this technic, he reported the histologic changes and hyperplasia of the chromophile cells in the anterior lobe of the hypophysis in a case of acromegaly. In this period were included six months of graduate study with Spalteholz in Leipzig, Germany, where (by reconstruction models) the fascia of the kidney was the subject of study.

From 1903 to 1924, with the exception of the war years, Dean Lewis taught surgery at Rush Medical College and carried on an increasing surgical practice at the Presbyterian Hospital. He became professor of surgery in 1920 and shared with Bevan the burden of teaching and direction of surgical activities.

It was in this stretch of years that he became exposed and succumbed to the wiles and attractions of travel. His reputation as a teacher and then as a surgeon and a contributor to progressive surgical thought grew steadily, and he was in demand throughout the Middle West and the West as a consultant surgeon, an operating surgeon and a speaker. His leadership in diffusion of sound surgical and pathologic knowledge was everywhere acknowledged. His many contributions concerned themselves with ductless glands, transplantation of tissue, bone tumors, neurosurgery and pathologic studies of the breast which were the results of both clinical and experimental studies. A noteworthy happening during this period was the first clinical use of ethylene as an anesthetic by Dr. Lewis at the Presbyterian Hospital. Subsequently, "Clinical Experiences with Ethylene Oxygen Anaesthesia" was published by A. B. Luckhardt, the discoverer of ethylene, and Dean Lewis, in December 1923.

As a teacher he provokes the greatest interest on the part of his students and colleagues, not only because he commands their respect for his clinical knowledge of the subject and the relation of the fundamental sciences and of medical history to it but because he conducts his clinic in the manner of a dialogue, which in the course of events demands answers to questions. This requires an agility of mind and a breadth of knowledge that few of his students and associates easily command, and, as a consequence, succeeding classes carry away, in addition to the clinical instruction, knowledge of many anatomic, pathologic and historical facts. The mere mention to his former students of the claw-hand and the lumbricales, "Madame" Dejerine, Rokitsansky, Nicoladoni or Astley Cooper will recall a few of the inquiries posed by an inspiring teacher.

The World War played an important role in Dean Lewis' life and in some ways may have been one of its happiest periods. Having a deep

regard for his country and for the soldiers of the line who were serving it, enjoying the society of his fellow men resourceful in unexpected situations and having real ability as an organizer and sufficient physical stamina to carry on, he made his service a notable one. Let the record speak for itself. He was commissioned a major in the medical corps of the United States Army in the spring of 1917 and was directed to organize Base Hospital No. 13 at the Presbyterian Hospital, Chicago. In December 1917 he was ordered to active duty with his organization at Fort McPherson, Ga., and shortly afterward was sent to the University of Michigan to conduct research on regeneration of nerves with Dr. G. Carl Huber. This work resulted in valuable information on the method of formation and prevention of neuromas. About May 1, 1918 he rejoined Base Hospital No. 13 at Camp Merritt, N. J. He sailed for France on May 18, arriving in June in Limoges, where Base Hospital No. 13 was permanently established. On July 8, he was sent to the American headquarters at Chaumont as the head of a surgical team consisting of three officers, two nurses and two orderlies and was assigned to work at Evacuation Hospital No. 7 at Coulommiers. After two weeks of very active service there he was transferred to Evacuation Hospital No. 6 at Chateau-Thierry, and on August 19 he was given command of the surgical service at Evacuation Hospital No. 5, which was also located at Chateau-Thierry. He continued to work with this hospital until the end of the war. During this period it was stationed at Juvigny from August 29 to September 14, taking care of the wounded from the Thirty-Second Division during the Verdun offensive. It was then moved to Villers-Cotterets, where it was set up in readiness to evacuate the wounded from the St. Mihiel sector. About September 29 the hospital was moved to LaVeuve, where it functioned until October 16, taking care of the wounded from the Second Division and from the Thirty-Sixth Division during the Champagne offensive. In the final days of the war his hospital was stationed at Staden, Belgium, working with the Thirty-Seventh Division and also with the Ninety-First. After the armistice Major Lewis was returned to Base Hospital No. 13 and was promoted to the rank of lieutenant-colonel of the United States Army. On December 28 he returned to the United States and was placed in command of United States General Hospital No. 28 at Fort Sheridan, Ill., where a large portion of the service consisted of treatment of nerve injuries and reconstructive surgical procedures. In August 1919 he was honorably discharged from the service, and some months later the United States government, in recognition of his services, accorded him the distinguished service medal.

After his discharge from the army he returned to his teaching and practice at Rush Medical College and the Presbyterian Hospital. In 1920 he accepted the editorship of the *ARCHIVES OF SURGERY*, which he

has continued to devote his energies to making one of the significant surgical journals of the day. He received offers from several medical schools to head their departments of surgery, but it was not until January 1925 that he accepted the professorship of surgery at the University of Illinois Medical School. This position he occupied for only six months, as he then accepted the professorship of surgery at Johns Hopkins University, where he succeeded Dr. William S. Halsted.

Dr. Lewis' work and accomplishments at Johns Hopkins are well known. He found himself among friends of many years' standing, who made him welcome and have ably supported his leadership in teaching, investigation and the training of young men. During this period Dr. Lewis has been particularly interested in and has contributed largely to the knowledge of the relation of sex hormones to tumor growth. He has edited the widely used "Practice of Surgery," published by Prior, and it is in these volumes that his own classic work on peripheral nerve injuries and regeneration of nerves appears.

I should like to quote a paragraph from a letter written to me by one of his Baltimore and Johns Hopkins Hospital colleagues. Speaking of Dean Lewis, he said, "His Friday clinics to the third and fourth year medical students were among the best and most scholarly presentations of surgical discussions that I have ever listened to. In these and in other teaching exercises he displayed a remarkable familiarity with the surgical literature of the whole modern world and a memory that was astonishing in its accuracy. He was particularly interested in the surgery of peripheral nerves, tendons, joints and bones, and in these fields, which many general surgeons rather neglect, he showed a mastery of the subject and an operative facility which was remarkable. During his entire time here he laid great emphasis on the relationship of anatomy to surgery and also on acquaintance with the unusual types of infections such as actinomycosis, sporotrichosis, etc. He turned out from the residency of the surgical service at the Johns Hopkins Hospital a number of extremely able young men, many of whom have secured positions of importance as teachers and staff members of universities and hospitals."

Emerson has justly said that too many times one is weighed down by facts and forgets principles. This imperfect record of Dean Lewis has perhaps had in it too much of facts and too little of the man. What stands out, then, above the facts? A host of friends who know the greatness of his soul, his loyalty, his matchless spirit, his love of sports, his great ability as a surgeon and his comradeship salute him and wish him long life and well deserved happiness.

# CHONDRODYSPLASIA

## REPORT OF A CASE

IRVIN ABELL, M.D.

LOUISVILLE, KY.

A patient came under my care in December 1939 with acute appendicitis. He presented such a multitude of skeletal tumors that after his recovery from the operation for appendicitis a study was made, and the case was deemed worthy of report. This was not so much because of the rarity of the lesion as because of the number and extent of the tumors, 91 being revealed on the roentgenograms. The condition conformed to the pattern of hereditary deforming chondrodysplasia in that numerous tumors were present, accompanied with skeletal deformities which arose between childhood and maturity and involved bones developed from cartilage. The component parts of each bony system, with the exception of those developed from membrane, showed such involvement.

In addition to the outward projections from the cortical regions giving rise to deformities, inward projections with the formation of central lesions were present. According to Geschickter and Copeland "the fundamental basis of the congenital disturbance is obscure, but deficiencies in the periosteum and a tendency for the perichondrium to persist and to function as such, together with precartilaginous connective tissue about the joints, seem to be responsible for most of the deformities."

## REPORT OF CASE

The patient, a man aged 25, was one of ten children. He stated that three of his brothers (not available for examination) had similar tumor masses and deformities, none as numerous or as large as his own. The remaining brother and his five sisters showed no visible evidence of the disease. There was a history of similar tumors in the father, but none had occurred in the mother or in the older generations of the family so far as he knew. His first bony deformity was noted by his parents when he was 1 year old. At the age of 11 years he was admitted to the Children's Hospital. The records show that in June 1925 bony tumors were removed from the left outer malleolus and from the lower end of the left ulna, microscopic examination of which confirmed the clinical diagnosis of benign osteochondroma. Roentgen examination at that time showed multiple exostoses of nearly all the long bones. Throughout childhood and adolescence numerous tumors appeared some of which grew steadily producing deformities about the larger joints of the extremities. During the last four years since reaching maturity, he had noted no further increase in size of any of the tumors except a no change in any of the deformities of the extremities. He gave no history of

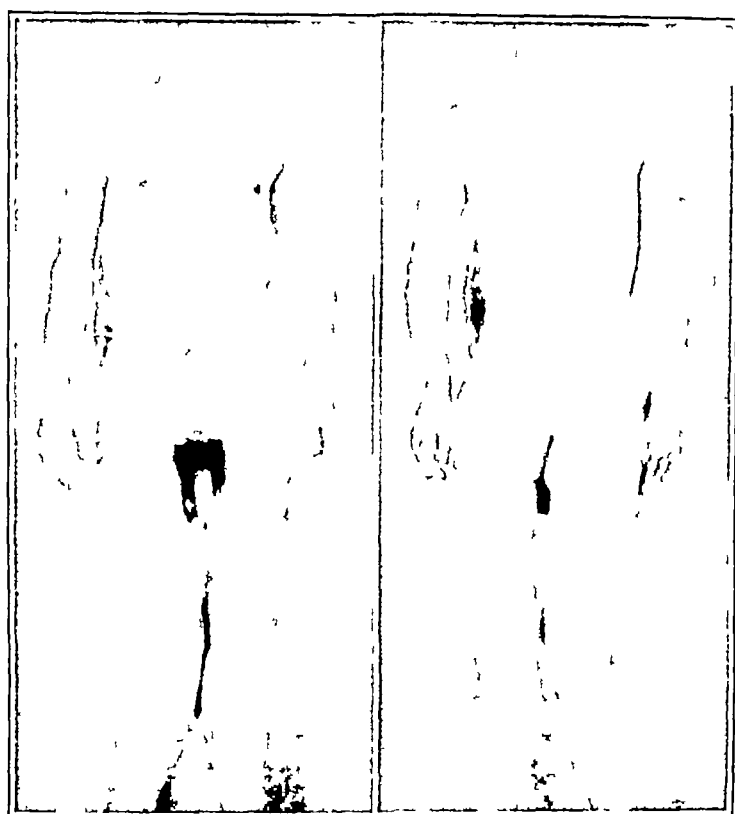


Fig 1—Photographs of the patient.

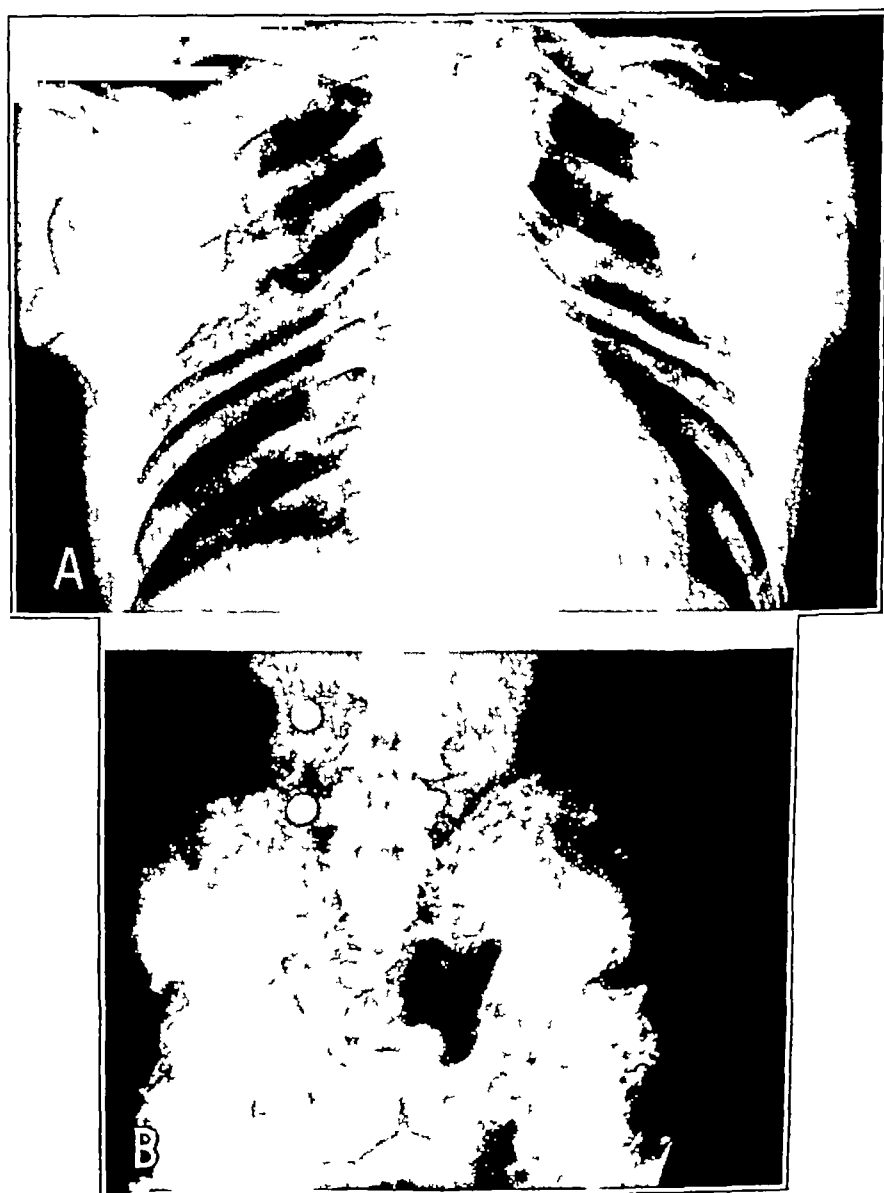


Fig 2—*A*, ribs and sternum, *B*, pelvis and hip joints

pain associated with the tumors and complained of no dysfunction other than a limp due to shortening of the right leg and a limitation of motion in the left wrist.

Physical examination revealed the heart, lung, blood pressure, blood and urine to be normal.

His height was 5 feet and 10 inches (177.8 cm). His weight was 132 pounds (59.9 Kg).

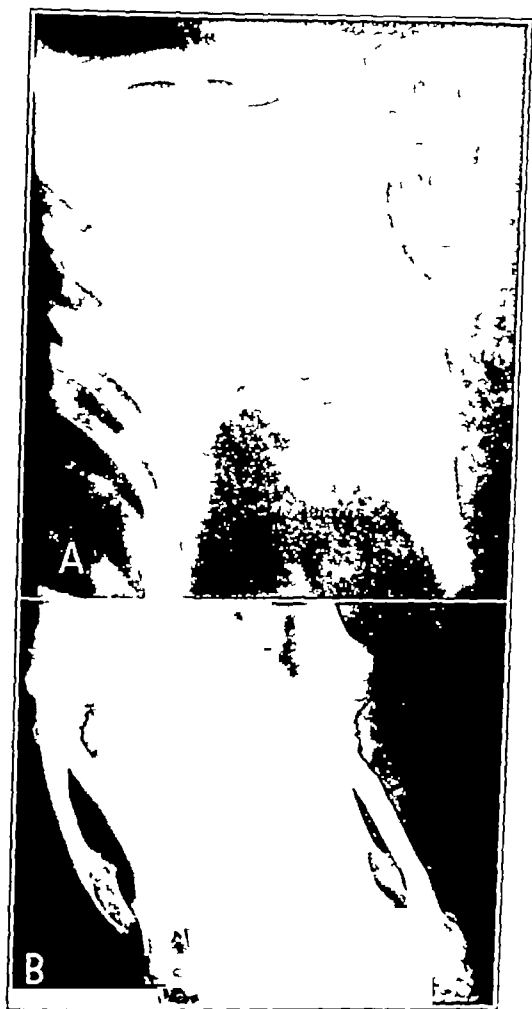


Fig. 3—*A*, left shoulder and upper part of humerus. *B*, left elbow, radius and ulna.

The head and neck were apparently normal with no visible or palpable bony deformities.

The patient stood with the pelvis tilted to the right and presented a moderate structural "right lumbar-left dorsal" scoliosis. There was some rotation of the

vertebrae, causing prominence of the right paravertebral region, especially noticeable in flexion. Motions of the back were free, with complete range of flexion and extension but slight restriction of lateral bending and rotation. There were small palpable irregularities and tumor masses on the medial border and posterior surface of the right scapula. The spine of the left scapula presented small palpable tumor masses, and its posterior surface also was nodular and irregular. There were numerous small conical masses arising from the ribs, but there was no marked deformity of the thorax as a whole. Palpable nodules were present over the pelvis.

All four extremities presented varying-sized, bony, hard tumor masses attached to the ends of the long bones. These tumors were of different shapes, some smooth and rounded, some nodular and some sharp. In several areas there were compound masses with multiple projecting processes. The tumors were not tender and were not attached to the skin or to the soft tissues. In addition to the tumor masses there were numerous deformities, the left upper and the right lower extremities being most severely involved. The lengths of similar portions of the extremities were different on the two sides, comparable measurements being as follows:

	Right	Left
Upper		
Acromion to olecranon	12 inches (30.4 cm)	11 inches (27.9 cm)
External condyle to radial styloid process	9½ inches (24 cm)	8½ inches (21.5 cm)
External condyle to ulnar styloid process	9 inches (22.8 cm)	6½ inches (16.4 cm)
Lower		
Anterior superior iliac spine to internal malleolus	34¼ inches (87.5 cm)	33¾ inches (91 cm)
Anterior superior iliac spine to patella	16½ inches (41.8 cm)	17¾ inches (45 cm)

*Left Upper Extremity*—There was a rounded, smooth bony tumor 1 inch (2.5 cm) in diameter attached to the medial aspect of the humerus, presenting in the axilla. There was no restriction of motion of the shoulder. The shaft of the humerus was smooth and straight. In the region of the elbow there was a small, irregular tumor mass apparently arising from the medial epicondyle. The head of the radius was prominent and palpably enlarged from tumorous overgrowth. The axis of the elbow joint and the carrying angle were approximately normal. Flexion and extension of the elbow were approximately normal. There were operative scars over the lower end of the radius and ulna, with rounded masses attached to the radius. The ulna was markedly shortened, throwing the wrist into about 40 degrees of adduction. Flexion and extension of the wrist were limited about 10 per cent, and there was over 50 per cent limitation of supination. There were several small pointed tumor masses arising from the metacarpal bones and the phalanges near the joints, causing slight deformity and limitation of motion. The fourth metacarpal bone was approximately ½ inch (1.2 cm) shorter than normal, the head being depressed and palpable in the palm.

*Right Upper Extremity*—There were a few palpable tumor masses arising from the upper end of the humerus, but there was no deformity and no limitation of motion of the shoulder. There were a 1 inch (2.5 cm) rounded tumor mass in the region of the medial epicondyle and 5 degrees of cubitus varus deformity of the elbow. Flexion and extension of the elbow were complete, but there was very slight limitation of pronation and supination. There was a small pointed tumor

arising from the distal third of the ulna, but there was no deviation from the normal relation between the radial and the ulnar styloid processes. There was no apparent involvement of the carpal or the metacarpal bones, but there were small tumor masses on the phalanges of all five fingers. There was very slight angulation deformity of the second, fourth and fifth fingers but no restriction of motion.



Fig 4—A, right shoulder and upper part of humerus, B, right elbow, radius and ulna

*Left Lower Extremity*—There was no apparent deformity around the left hip. There were diffuse grating on motion of the hip and limitation of abduction to about 30 degrees. There was no limitation of flexion, extension or rotation. The greater trochanter was in its normal relation but there was palpable irregular enlargement of the upper end of the shaft and the neck of the femur. The thigh



was apparently normal, but in the region of the knee there were fairly large rounded nodules palpable on the medial and lateral aspects of the lower end of the femur. There was complete range of motion at the knee. There was a large compound tumor mass about 3 inches (7.6 cm.) in diameter on the medial aspect of the upper end of the tibia, causing about 10 degrees valgus offset of the shaft on the diaphysis. There likewise were small rounded protuberances over the upper

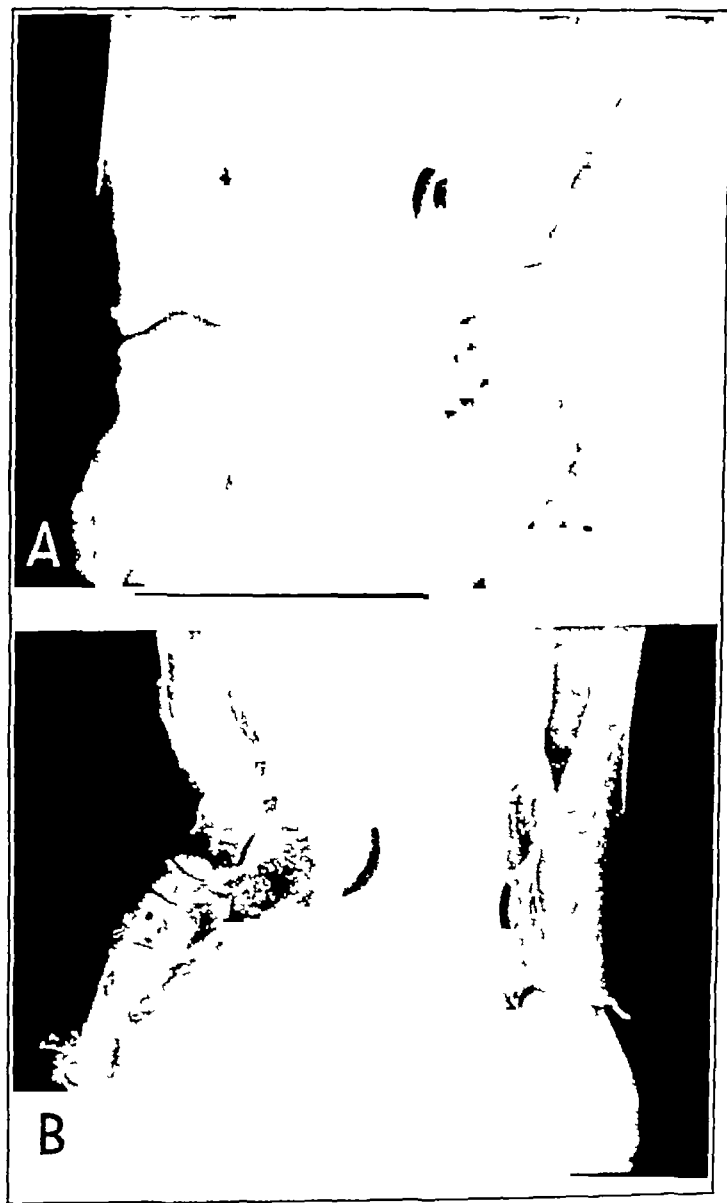


Fig 5—*A*, left knee, *B*, left ankle and foot.

end of the fibula. There were numerous rounded and pointed masses around the lower ends of both the tibia and the fibula, but there was free motion of the ankle joint. However, marked talipes valgus was present. The foot was broad and short, and a few irregularities were palpable in the metatarsal bones. The great toe was apparently normal. There was a severe congenital anomaly involving the other

toes. The third and fourth were displaced dorsally above the second and fifth, and there was a partially developed supernumerary digit between the third and the fourth.

*Right Lower Extremity*—There was no restriction of motion of the hip, but there was a compound tumor mass about 4 inches (10 cm) long and 3 inches (8.6 cm) wide, palpable posterior to and below the greater trochanter. The thigh



Fig 6—A right knee B right ankle and foot

was normal, but there was a severe deformity of the right knee due to tumor masses arising from the lower end of the femur and the upper end of the tibia. The knee lacked 15 degrees of complete extension. There were 20 degrees of valgus deformity and about 15 degrees of external rotation at the knee. There were large compound tumor masses arising from the medial side of the femur and tibia.

causing discoloration of the skin over their prominences. There also was marked enlargement and dilatation of the saphenous vein. There were small tumor masses on the lateral aspects of the lower part of the fibula and the upper part of the tibia. In the region of the ankle there were scars from previous operative removal of tumor masses, but there were numerous small nodular masses still present around both malleoli. There was slight talipes valgus of the foot but no other deformity, and few small tumor masses were palpable.

#### SUMMARY

A case of chondrodysplasia in a man aged 25 is presented

# THE PLACE OF THE GASTROSCOPE IN THE DIAGNOSIS OF LESIONS OF THE STOM- ACH AND OF THE DUODENUM

DONALD C BALFOUR, M.D, F.R.C.S  
ROCHESTER, MINN

The great contributions which have been responsible for the present knowledge of lesions of the stomach and of the duodenum have been the facts disclosed by surgical treatment of these lesions during the life of the patient, the development of roentgenology, which shows by indirect means the site and character of these lesions, and the development of the flexible gastroscope. The development of endoscopy has been a spectacular feature of modern diagnostic methods, and those instruments which have for their purpose the visualization of cavities of the body are some of the most ingenious and useful examples of the instrument maker's art. It was inevitable in all this development that some satisfactory means should be devised for visualizing the interior of the stomach. For many years physicians had to be content with an inadequate, rigid instrument, but the flexible gastroscope has opened a new field and has proved that it is possible to obtain a satisfactory view of the interior of the stomach in almost all cases. It is difficult to visualize two portions of the stomach—a narrow strip of the posterior wall, along which the gastroscope rests and which cannot be separated far enough from the lens of the gastroscope for adequate visualization, and a small segment of the lesser curvature of the antral portion, just beyond the angle. There are a few cases in which the difficulties in using the instrument are such that this type of examination is contraindicated, but these cases form only a very small per cent of the cases in which gastroscopic examination is advisable. Enough experience has now been obtained in the use of this instrument to give some idea of its value and its contributions to knowledge of lesions of the stomach and of the duodenum.

When it was learned that the gastroscope would give a satisfactory view of the interior of the stomach, one of the first questions which the members of the medical profession sought to answer was in relation to gastritis. It was generally accepted that gastritis is the most frequent of all pathologic conditions of the stomach, but there was vagueness as to how gastritis should be classified from the standpoint of symptomatology.

and the relation of the symptoms to the various stages. Similarly, a satisfactory answer had not been given regarding the relation of gastritis to organic lesions of the stomach, particularly to ulcer and carcinoma. The claim made by many observers that gastritis is a precursor of ulcer and is the chief factor in disappointing results following operation for ulcer has been difficult to evaluate. The basis for this claim is somewhat theoretic, but certain clinical and experimental evidence supports it. For example, it has been shown that the use of cinchophen in animals produces a sequence of events culminating in chronic ulcer, in which gastritis in various stages associated with multiple ulcerations precedes the formation of the chronic lesion<sup>1</sup>. Any method which would permit one to identify these different stages of gastritis clinically, to observe the circumstances under which they develop, to correlate the symptoms with the pathologic picture and to determine whether these changes are liable to be followed by chronic ulcer would be a great contribution toward a more intelligent understanding of both benign and malignant lesions of the stomach. It is in this respect that the flexible gastroscope offers so much. As yet there is much to be determined, but a vast amount of information is rapidly accumulating which may be applied to a better understanding of these questions.

In cases of duodenal ulcer the gastroscope has not as yet been of much value, since it is impossible to visualize the duodenum, and only those changes which are secondary to an ulcer can be identified. But in this respect the gastroscopic examination may be valuable, for the decision as to treatment may be determined by the finding of a deformity secondary to ulcer. Similarly, gastroscopic examination may disclose important data in respect to results of operation for duodenal ulcer. This is true in cases in which disappointing results follow surgical management of ulcer, regardless of the operation which has been carried out, and particularly in those cases in which operation involves the use of the jejunum either in gastroenterostomy or after partial gastrectomy. One of the puzzling problems in connection with surgical treatment of duodenal ulcer has been that of interpretation of some of the symptoms which may occasionally recur after operation. In this respect the gastroscope is proving to be a welcome aid in obtaining accurate information, for the skilled gastroscopist is enabled not only to study the operative stoma, which may be under inspection, and report on its actual appearance but to study the adjacent portions of the loops of the intestine which were associated with it.

In cases of gastric ulcer the chief value of the gastroscope is in the differential diagnosis of benign and malignant ulcer. Enough evidence

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<sup>1</sup> Stalker, L. K. *Experimental Cinchophen Peptic Ulcers*, Thesis, University of Minnesota Graduate School, 1937.

has now accumulated to show that by this method such lesions can be studied so directly as to give valuable information in determining whether or not the ulcer is malignant. I do not believe that the method has reached the point of absolute dependability, yet the knowledge which has been acquired in the relatively short time in which the instrument has been used seems to indicate that, more than any other method except microscopic examination, it will probably contribute to the surgeon's ability to differentiate these lesions. Similarly, the method makes it possible to locate other, smaller lesions which may have been overlooked in a case of gastric cancer. It is also true, although of rare occurrence, that roentgen examination may fail to detect a small cancer in the fundus of the stomach, yet the lesion may be readily identified by a competent gastroscopist. The gastroscope also permits identification of the type of cancer and enables one to determine whether multiple lesions are present. Of the greatest importance is the fact that it may give information as to the operability of the growth.

It is in the study of the stomach after operation that the flexible gastroscope has such interesting possibilities. Until this instrument was developed to a point at which a satisfactory inspection of the stomach could be made, the interpretation of symptoms persisting after operations for benign lesions of the stomach was, to some extent, conjecture. It is probably for this reason that there was such a great discrepancy in the figures reported from various clinics as to the results of various types of operations, since the relation between symptoms and pathologic change in the stomach after operation is on a much less definite basis than when no operation has been carried out. While roentgenology contributed much knowledge in this particular group of cases, the roentgenologist was the first to recognize the fact that there were definite limitations in the story the roentgenoscope and the roentgenogram could tell of the postoperative condition of the stomach, particularly in those cases in which extensive reconstruction operations had been part of the surgical procedure. The increasing accuracy of the flexible gastroscope in enabling one to view practically all parts of the stomach has been a boon to both the clinician and the surgeon in evaluating symptoms following operation and also in providing evidence as to the effectiveness of various types of operation. Some surprising points have already been brought out by Schindler and his associates<sup>2</sup> and by Moersch and Walters<sup>3</sup> in gastroscopic studies after operation.

<sup>2</sup> Schindler, R., and Gold, R. L. *GastrosCOPY in Gastric Carcinoma Especially in Its Early Diagnosis*, Surg., Gynec. & Obst. **69** 1-17 (July) 1939.  
Schindler, R., Necheles, H., and Gold, R. L. *Surgical Gastritis: A Study of the Genesis Found in Resected Stomachs with Particular Reference to the So Called "Antral Gastritis" Associated with Ulcer* *ibid.* **69** 281-285 (Sept.) 1939.

<sup>3</sup> Moersch, H. J. and Walters, W. Unpublished data.

The latter observers recently studied a series of more than 100 cases in which various types of operations were carried out. Some interesting observations were made possible by this study, particularly in relation to the incidence of gastritis, which has been such a controversial point in regard to the relation of gastritis to persisting symptoms after operation. For example, in about a third of the cases in which gastroenterostomy was done for duodenal ulcer and in which sufficient symptoms persisted to require a subsequent thorough examination, gastroscopic study revealed that the stomach was apparently entirely normal. Although Schindler, in his report of postoperative gastroscopic examinations, noted a much smaller percentage of normal stomachs after operation, Moersch and Walters pointed out that this disagreement is probably due to difference in opinion as to what constitutes normal gastric mucosa and early changes of gastritis. They also pointed out that the gastroscopic picture may change markedly after an acute infectious process or an indiscretion in diet. The feeling that "the longer the period which is allowed to elapse between a surgical procedure on the stomach and gastroscopic examination, the less likely is gastritis to occur" was not found true in this series. The question of what accounts for gastric distress in those cases in which the stomach is normal as far as the gastroscope is concerned introduces the fact that functional disturbances are apparently frequently the predominant elements in the symptoms both before and after operation. Approximately two thirds of the patients who were subjected to gastroenterostomy for duodenal ulcer and in whom completely satisfactory results did not follow the operation showed evidence of gastritis, and almost every variety of gastritis might be seen in the same stomach. Moersch and Walters pointed out that one variety, which they classified as erosive gastritis, seemed not only to produce distinct symptoms but to respond satisfactorily to therapeutic management. This type of gastritis is characterized by multiple small erosions. In a small group of cases in which gastroenterostomy was done for duodenal ulcer there was a history of gastric bleeding at some time after the gastroenterostomy, and the clinical history was suggestive of gastrojejunal ulcer. In the cases in which another operation was performed the lesion which was found was erosive gastritis associated with gastrojejunitis rather than a typical gastrojejunal ulcer. The appearance of the stomach after partial gastrectomy is particularly interesting because of the still debated question as to the permanent effectiveness of partial gastrectomy in dealing with duodenal ulcer. In a third of these cases no abnormality was detected in the gastric or the jejunal mucosa, and in this group, as in cases in which gastroenterostomy was performed, satisfactory control of the symptoms was obtained by medical measures. There was a high incidence of erosive gastritis,

but fortunately this also seemed to respond satisfactorily to adequate medical management. In a group of cases of gastric ulcer in which an opportunity was given for subsequent endoscopic examination, the majority of the patients had been subjected to excision of the ulcer and gastroenterostomy, and a smaller number had undergone a partial gastrectomy. There apparently was approximately the same relation of gastritis in this group of cases as was found in the preceding groups, with the additional finding of carcinoma in a sufficient percentage of cases to illustrate the close relation of gastritis and gastric carcinoma.

In a general way, the study which Moersch and Walters have recently completed has given important information as to the appearance of the stomach after various types of operations for various lesions. The important feature of the study is that the high incidence of gastritis is a probable factor in the persistence of symptoms. Further studies of the stomach after operation will probably, if carried out on a sufficient number of patients who have not had recurrence of symptoms after operation, furnish further important information on this interesting point. Therefore, it may be anticipated that it will be possible to evaluate much more accurately the cause of symptoms following operation for peptic ulcer and to deal more intelligently with them.

Permission was granted by Drs. Moersch and Walters to use statistics prepared in connection with their postoperative study of the stomach, which has not yet been published.



## BORDERLINE PROBLEMS IN THE DIGESTIVE FIELD

THOMAS R BROWN, MD

BALTIMORE

Notwithstanding the increasing penetration of surgery into many other fields, cardiovascular, respiratory, renal, neural and endocrine, I feel sure that the digestive tract presents by far the most borderline problems, in which one must decide in each individual case whether surgical or nonsurgical treatment is the more likely to bring about cure or improvement. To operate or not to operate for peptic ulcer, gastric or duodenal, disease of the gallbladder, chronic appendicitis, cancer of the esophagus, stomach or small and large intestine or nonspecific ulcerative colitis—that is the question, and, if operation is decided on, when to operate, what operation to perform and who is to operate. On the proper answers to these questions depend in large measure the end results in each case.

While the main purpose of this short paper is to discuss treatment, it is axiomatic that for the optimum results correct diagnosis or, at least, a diagnosis of maximum probability is essential. But diagnosis of many intra-abdominal conditions is often extremely difficult, and it is only by the closest cooperation of internist and surgeon as well as by utilization of all appropriate technical methods that error can be reduced to a minimum. One may like to agree with Neusser that “the history of the case should give us our correct diagnosis, the physical examination and laboratory findings should be merely confirmatory” or to believe with Hilton that “every pain has its distinct and pregnant significance if we will but carefully search for it,” but in the abdominal field this is sometimes not enough. Nevertheless, it is obviously essential that in every case a careful and thoroughly digested history should be taken and an especially painstaking analysis should be made of the symptom *pain*—the symptom that usually brings the patient to the physician—for in many cases it is the best means of reaching a correct diagnosis or at least of obtaining a valuable clue.

But pain is often a fragile reed on which to lean, for there are few if any pain fibers in the viscera, and with a viscerosensory reflex as the best explanation of abdominal pain, with the similarity of the nerve supply to abdominal and thoracic organs, with the close proximity of the various abdominal organs to each other (for example, the gallbladder, the pylorus, the duodenum, the hepatic flexure or the appendix, the

right ovary and tube and the ureter. The fact that the third perigastric all that separates the lower thoracic from the upper abdominal organs is it any wonder that the pain picture of these organs often overlap, that referred pain is so common, and that the interpretation of a given pain is difficult at times?

It is worth remembering in this connection that De Lee in his "Practice of Surgery" mentioned several cases which simulate the pain of disease of the gallbladder and several which simulate that of acute appendicitis, and in these cases there are those unpredictable variables, the enormous variations in individual response to stimuli and the large role the psyche plays in the interpretation. Thus, while each case should be studied with the most meticulous care by the internist as well as the surgeon for each approaches the problem from a somewhat different angle and each may discover something which the other may have missed, and while each case must be regarded as presenting a special problem of research to be attacked by "that insatiable intellectual curiosity that differentiates man from the beast," there will probably always remain a small group in which one is obliged to agree with Charles Mayo that "sometimes our best means of diagnosis is the memory of what we found in the abdomen when an exploratory operation was performed months or perhaps years previously upon a patient presenting a similar clinical picture."

Many of the organic diseases of the digestive tract are obviously potentially "surgical" as regards treatment. But surgical treatment is a two-edged sword—it takes away but it also gives, it removes organic disease—ulcer, diseases of the gallbladder or appendicitis—at a surprisingly low mortality rate in the hands of a skilled surgeon, but with the best technic there is always the possibility of formation of adhesions, bringing about greater or less obstruction or impairment of function, while certain operations in their very essence leave behind an abnormal physiologic picture—for example, gastroenterostomy, ileostomy, ileosigmoidostomy or cholecystogastrostomy. With care and time certain of these unphysiologic states may produce few or even no symptoms, but sometimes the state of the patient may be no better than before he was treated surgically. From a month's census of all new patients admitted to this clinic, one fourth of the total number had been previously operated on but had returned complaining of the same symptoms or of new symptoms.

On the other hand the surgeon is prone to forget that functional disturbances do not disappear with the removal of their organic cause, it may take months or even years of careful postoperative treatment to conquer these functional habits—pylorospasm, hyperchlorhydria or gastric or intestinal dyspepsia—and it is lack of realization of this that

has converted many potential cures into relative or complete failures. The surgeon is keenly aware of the immediate results of the operation, results due in some measure to the rest and proper care in the hospital incidental to the operation. He is far too often ignorant of the late results of supposedly successful operations, for, if old symptoms persist or new symptoms arise, the patient frequently does not return to the same surgeon but consults an internist or another surgeon.

I shall discuss briefly certain of these borderline conditions. It is axiomatic that the more definite the need for surgical attack, the greater the likelihood of a permanently successful result. Thus, the percentage of cures is much higher in cases of cholelithiasis with frequently recurring attacks of pain, in cases of gastric or duodenal ulcer with gross organic obstruction and in cases of acute or recurrent appendicitis than in cases of chronic cholecystitis without stone, nonobstructing peptic ulcer or chronic appendicitis. The greater the need, the more clearcut the picture, the better the end result!

#### PEPTIC ULCER, GASTRIC OR DUODENAL

The question of peptic ulcer was once the great battleground

"Each champion to the other's virtue blind  
And thinks his treatment only cures mankind",

but it is now the scene of few controversies, for the lion and the lamb lie down peacefully together, and the lamb is often more bloodthirsty than the lion. The borderline problems in this field, however, are still interesting.

How much do the obstructive symptoms depend on organic stricture which is "surgical", how much on inflammation, spasm and edema, which may be relieved by nonsurgical measures?

How many large hemorrhages should a patient have before being operated on? In most cases two or three, not more. Should the operation be performed at the time of the bleeding because the source of many hemorrhages is difficult to find in the interval between bleedings, being often a minute ulcer or erosion, often tucked between mucosal folds?

How often is potential malignancy a reason for operation? Never in the case of duodenal ulcer, but certainly always in the case of gastric ulcer if the lesion does not respond to treatment, if occult blood persists in the stool or if the roentgen defect is large and persistent under a regimen of rest, soft diet and time. And yet in my series only 5 per cent of gastric ulcers became malignant, in two relatively recent German series, only 1.8 per cent and 3 per cent respectively.

If there are perigastric or periduodenal adhesions which do not obstruct but which render normal physiologic function difficult, how long should one try dietetic and physical measures before advising operation?

Many patients can be kept surprisingly comfortable if they are willing or able to follow certain rules as regards diet and general hygiene, sometimes supplemented by simple medication, but with the American patient, at least, this is not easy, he chafes at restrictions, he demands quick results. Just as in the cure of acute ulcer, any one, with a very simple diet, can usually quickly relieve the symptoms. Very few have the personality and the persistence to persuade the patient of the necessity of a long course of after-treatment. Yet, if operation is finally decided on, this is the type least likely to respond satisfactorily.

If operation is decided on, what shall the operation be? Gastroenterostomy is brilliantly successful in cases of gross obstruction, but in my experience it is usually disappointing when there is no obstruction or only very slight obstruction. It drains the stomach and gives partial rest to the ulcer, but it does not stop hemorrhage, and it is essentially nonphysiologic. It is not without justification that the Germans speak of "*diese Krankheit-Gastroenterostomie*" or that Horder said, "the operation should be regarded as the first step in treatment and not the last."

Should one, in certain cases of gastric ulcer in which resection is extremely difficult, utilize jejunostomy more, so that one may see whether long rest and freedom from local irritation may bring about a cure? In my hands, the best results have been obtained by the smaller resections—pyloroplasty (possible only in a relatively small percentage of cases and performed well by the very few), gastroduodenostomy, the Polya operation, etc., but a great many able surgeons believe that in very large resections lies the only hope not only of curing ulcer but of preventing its recurrence and that it is only by removing the entire acid-stimulating portion of the stomach that this can be brought about. Are they right? Time only can tell.

The treatment of ulcer is a very complicated problem, and the key has not yet been found, for ulcer is not only a local problem, it is constitutional, it is a state of body and a state of mind as well. Every one knows the enormous role that emotional disturbances play in the recrudescence and possibly even in the origin of ulcer. It is known that centers of parasympathetic control lie in the hypothalamus, that stimulation of this area in animals causes increase of hydrochloric acid secretion and of gastric motility, that cardiospasm and megaesophagus arise experimentally if all branches of the vagus nerve to the stomach and the duodenum are cut but not if the pyloric branch to the vagus is spared and that with certain intracranial lesions notably pituitary and hypothalamic peptic ulceration may occur. Does this suggest that in certain cases vagotomy or vagectomy should supplant the more gross operation on the stomach and duodenum in the treatment of ulcer?

## CHRONIC APPENDICITIS

Does such a condition exist? Some surgeons believe not, but I am sure they are wrong. Why should the appendix be denied the privilege of chronic disease? Every other organ enjoys it. But the diagnosis as usually made is undeniably wrong. In most cases it is but a part of a low grade inflammatory process involving the terminal part of the ileum, the cecum and the ascending colon, usually associated with visceroptosis, chronic constipation and an atonic, thin-walled cecum. Appendectomy is harmful and simply intensifies the patient's symptoms.

But I am equally sure that there is a very small group of cases of true chronic inflammation, often with no history of an acute attack, sometimes with a vague memory of an abdominal attack (usually undiagnosed) many years before. Gaither and I reported 47 such cases, in which the symptoms were rarely in the right lower quadrant of the abdomen, but usually were referred to the epigastric region and simulated a hyperacid, hypersthenic dyspeptic syndrome, a periodic syndrome characteristic of peptic ulcer or (very occasionally) of colitis. The fact that these symptoms, previously refractory to treatment, entirely disappeared after the appendectomy and that marked gross and microscopic pathologic changes were observed made us feel that the cases were true examples of chronic appendicitis.

We were much helped in our diagnosis by serial fluoroscopic studies especially those extending over several days. There was visualized an appendix of abnormal size or, more often, of abnormal and often extremely bizarre form, and one in which the barium sulfate remained for a long time, in 1 case more than a week, after active purgation with magnesium sulfate.

## CANCER

For cancer of the digestive tract nonsurgical treatment is purely—and poorly—palliative. In this field, at least, deep high voltage roentgen and radium therapy has been bitterly disappointing except in a few rare instances, usually of conditions of mesoblastic origin, while colloid selenium and colloid lead are equally ineffective. But to increase the percentage of cures (and cures have been none too frequent up to the present) it is essential that one make an early or at least a relatively early diagnosis, and this is extremely difficult. Pain is a rare early symptom in cases of cancer of the digestive tract, and one must look elsewhere for clues. If one looks for palpable tumor, for anemia or for marked loss of weight one will usually have waited too long. There is one and only one means that I know of, that is, to suspect any "digestive" symptom—progressive or intermittent dysphagia, gastric dyspepsia, increasing constipation, alternating constipation and diarrhea, attacks of intestinal colic appearing without cause and not yielding.

symptomatic therapy, especially it associated with slight loss of weight, some loss of appetite and, perhaps most important of all, persistent traces of occult blood in the stool (for while hemorrhage is rare, constant slight bleeding is very common) These symptoms usually appear in middle or later life, but in younger persons carcinoma is not unknown, even that slowly growing form usually met with in older patients. Cancer of the digestive tract, as a rule, is of slow evolution. There must always be a long silent period, and what one believes to be the first or second act in the drama may be in reality the third or fourth.

In my opinion, the remarkable feature of neoplasm of the digestive tract is the striking rarity of a previous history of digestive disturbance, and I cannot agree with those who think that gastric carcinoma develops in most cases from achylic gastritis. In a large series that I studied, 5 per cent of the patients gave a history suggesting peptic ulcer, and less than 15 per cent had had gastric dyspepsia, more than 80 per cent had had absolutely no previous history of gastric indigestion, the condition comes "out of the blue," "*wie ein Dieb beim Nacht*." If suspicions are aroused, it is obvious that all the essential tests should be made—gastroscopic, esophagoscopic, sigmoidoscopic and thorough fluoroscopic and roentgen studies, together with examination of the blood and urine, of the stool and of the gastric and duodenal contents. In no instance of suspected pathologic change should one fail to palpate the abdomen in a hot bath or to make a digital rectal examination. From some of these studies one may get definite confirmation of one's tentative diagnosis, in other cases no information of vital importance will be obtained, but even in the latter group, if the symptoms persist, if there is occult blood in the stool and if there is loss of weight, I feel that an exploratory laparotomy is absolutely justifiable. It is frequently wiser to operate on the basis of a well grounded suspicion than to wait until a definite diagnosis can be established. On the other hand, a large growth is not necessarily inoperable. I have seen many large gastric neoplasms with no evidence of metastases to the liver or the regional lymph glands and small growths with extensive metastases. Each case must be a law unto itself. Even when complete removal is impossible, relief may frequently be obtained, not always by short circuiting but sometimes by resection.

Esophageal neoplasm, with its early obstructive symptoms, its slow rate of growth and its tendency to late metastasis, should be a favorable field for the surgeon, but the technical difficulties have so far proved insuperable. I feel confident, however, that they will be overcome, probably as a by-product of the amazing improvement in surgical treatment of the lungs and mediastinum.

In the case of the stomach, early diagnosis is most difficult because of the predilection of cancer to originate in the silent area, the lesser curvature. An increasing number of cures lasting five years or more are being reported, while in the large bowel, where early diagnosis is much more likely, the results are surprisingly good.

In the case of carcinoma of the pancreas, should one do nothing or at most advise a cholecystogastrostomy or a duodenostomy to relieve the symptoms and possibly prolong life, or should one advise resection, realizing that, although the operation is dangerous, if it is successful long life is possible with the proper diet, and with administration of insulin and possibly pancreatic extract? I am sure that pancreatic malignant disease could be diagnosed much earlier if one became "pancreas-minded," if one thought of such diseases as the possible cause of certain symptoms referable to the upper part of the abdomen, periodic attacks of persistent pain in the back for which no explanation can be found in the stomach, the duodenum, the gallbladder or the intestine. Studies of the stool and quantitative estimation of pancreatic ferments in the duodenal contents or in the stool can be of help in this connection.

The gallbladder is perhaps the most fertile field for honest controversy. There is, of course, no question that operation is the only treatment for empyema and the wisest for cholelithiasis with frequently recurring attacks of severe pain. But in other conditions there is much difference of opinion. Should one operate immediately for acute cholecystitis? Many surgeons think so and claim that the mortality is no greater than with an interval operation, but this is at variance with certain German statistics showing the mortality to be three times as great. I cannot help but feel that a waiting policy is wiser if the patient is in a hospital where he or she can be watched with scrupulous care and where there are facilities for frequent leukocyte counts.

Graham, a few years ago, said that he had not operated on an "acute gallbladder" for several years. I have had a few cases of perforation, but the all-embracing arms of the omentum have made of it only a small localized process in no wise affecting the subsequent interval operation. In the only case of bile peritonitis that I have observed for many years the condition was due to the slipping of a ligature on the cystic duct after a cholecystectomy. In the case of demonstrable but symptomless gall stones, I believe that the mortality risk of operation is far greater than that of the possibility of their causing malignant disease of the gall bladder. Cholecystectomy unquestionably is the operation of choice, but there is certainly still a place for cholecystostomy in that small group of cases in which there is evidence of marked infection in the liver and in the intrahepatic biliary tree as well, for long external drainage or a cholecystogastrostomy or cholecystoduodenostomy may be the

means of curing these conditions, and a valuable crutch may have been removed with the cholecystectomy.

There is possibly mild hepatitis in most cases of disease of the gallbladder, and there is much evidence in favor of the view that in most cases the liver is the primary seat of infection, but in most instances this condition is unquestionably relatively slight and can be improved or even cured by the better biliary drainage following cholecystectomy and the proper postoperative care.

After cholecystectomy, however, there is always the possibility of certain sequelae—adhesions or stone or stricture of the common duct—and in certain cases these may reproduce the original, or inaugurate a new, set of symptoms. In a group of 84 private patients for whom I felt that operation on the gallbladder was indicated and on 63 of whom cholecystectomy was performed, a careful subsequent survey, in many cases by personal questioning and reexamination made by my associate, Dr. Howard, showed that 44 per cent of the patients were completely cured, 16 per cent relatively cured, 18 per cent improved and 20 per cent not improved.

Finally, what is to be done in that large group of cases in which there are vague dyspeptic symptoms and in which the diagnosis is usually made by the radiologist rather than by the clinician? There is no question that chronic cholecystitis is very prevalent. Some surgeons say that more than 50 per cent of the abdomens opened by them in older persons show definite evidence of cholecystic disease. I am quite sure that in this type of case operation should be the last resort and should be resorted to only after the failure of a long course of nonsurgical therapy. The objectives are relatively simple—to prevent reinfection as far as possible, to minimize the chance of duodenitis, to promote free biliary flow and to correct constipation. The teeth, tonsils and sinuses should be checked, careful habits of eating should be insisted on and a simple diet prescribed. There are no better methods to promote biliary drainage than the utilization of these normal physiologic stimuli, with frequent feedings, large amounts of the simple fats, butter, egg yolk and olive oil (to be avoided only if jaundice is present whether stones are present in the gallbladder or not), large amounts of soft greens and fruits and water in considerable amounts. If additional help is needed to prevent constipation, there is nothing better than a "morning saline."

In the vast majority of cases I am certain that these measures are far preferable to drainage through a duodenal tube and are equally effective. If all these measures fail, one may be obliged to call in the surgeon, but he should not be too optimistic as to the results of operation, for this is the group in which failures are many and complete successes few.



Perhaps certain other fields in the digestive tract should be mentioned in which borderline problems may arise nonspecific ulcerative colitis, chronic anebiasis, for which cecal and appendical resection may occasionally be necessary to bring about a permanent cure, terminal ileitis, for which sooner or later operation is usually indicated, and even visceroptosis for there are a few, fortunately a very few, surgeons who still harbor the chimeric illusion that suspending a fallen stomach or fixing a movable cecum will bring back normal function

The cause of nonspecific ulcerative colitis is not known. There is no specific cure, and treatment is purely symptomatic. Vaccines and serums, nonspecific protein shock, various drugs given by mouth or by rectum (sulfanilamide, iodine, azochloramid, acriflavine, gentian violet, oxygen), while they occasionally cause apparent temporary improvement, have not proved curative. Treatment is purely symptomatic: general hygiene, rest, a high caloric, relatively low residue diet, in some cases with the addition of certain vitamins, iron if the patient is anemic, drugs to control the diarrhea and occasionally blood, salt, calcium or sugar given by vein or subcutaneously.

While in certain cases these conditions remain mild local problems with relatively long periods of remission, in practically all the cases of severe involvement the question of surgical treatment usually arises. What has it to offer? In the "severe fulminating cases," often associated with severe and frequent hemorrhage, one must have recourse to it, although unfortunately only too often it is unsuccessful. In cases of moderate or even severe involvement I am sure one only too frequently postpones operation too long. One hopes that each patient will be the one susceptible to the drug or serum, one hopes that the specific cure is just around the corner. And yet I am sure that if one operated earlier in certain of these cases and gave the intestine the complete rest which is the only hope of real cure, certain of the ileostomies could be closed after six, twelve, eighteen or twenty-four months with a *restitutio ad integrum* of the intestine. While apparently complete repair may take place in cases of very extensive pathologic change in most cases too much damage has already been done to the colon, and a permanent ileostomy must be faced, with the intestine left in or a subsequent colectomy performed. Many prefer the latter. I have found that it is unnecessary in most of my cases, as the diseased intestine becomes strangely quiescent after the fecal stream has been diverted. Ileo sigmoidostomy is, alas, rarely possible in cases of ulcerative colitis, for the rectum and the lower part of the sigmoid flexure are involved in the vast majority of cases, (probably well over 95 per cent).

I have tried to present briefly certain of the, to me at least, interesting, borderline problems in the digestive field, problems frequently difficult

to solve, with results only too often unsuccessful or not completely satisfactory whether surgical or nonsurgical methods are employed. The surgeon, because of his brilliant success with the 'acute abdomen' is somewhat too optimistic as to the results of surgical attack on the "chronic abdomen." The internist often persists far too long in medical measures which are obviously not bringing about permanent improvement, and frequently this delay makes surgical treatment when it is decided on, more difficult and the results less satisfactory.

The surgeon's viewpoint should be physiologic as well as morphologic. He should think of function as well as form. The physician should realize that functional disturbances often have an organic basis and that the attack on the former is often unsuccessful because of his neglect of the latter. It should be obligatory for him to be present at the operation, the knowledge, pleasant or unpleasant, that this "autopsy in vivo" will bring, is always valuable and sometimes salutary. But to get the best results there should be close cooperation between the surgeon and the internist in diagnosis, in the preoperative care, in the postoperative treatment and even in the operative treatment of the patient.

# DISEASES PECULIAR TO CIVILIZED MAN

GEORGE CRILE, M D

CLEVELAND

With the increased pace to which civilized man must adapt himself, there are several diseases accompanying his highly energized manner of living. Frequently the physician is called on to treat diabetes, peptic ulcer, essential hypertension, exophthalmic goiter, diseases of the coronary arteries and nervous and mental diseases. These conditions are exceedingly rare in primitive man and are uncommon in the lower ranks of civilized man. The more highly civilized man becomes, the more prevalent they seem to be.

As man has become less concerned with fighting, hunting and other predominantly physical activities and more concerned with mental activities, the characteristic mental and emotional mechanism has continued to increase relatively in size and in dominance until there are now also increasing the diseases I have mentioned, which are in large part due to overactivity of the kinetic system. Evidence indicates that the kinetic system may, by its excessive activity, interfere with the health and the function of certain other organs of the body. The "brain-adrenal-thyroid-sympathetic system" in an increasing number of cases is becoming hyperactive, establishing a state of such excessive activity as may fittingly be termed hyperkineticism. The background of these diseases is laid in the racial history of man, in man's phylogeny. It is only in this way that it has been possible to understand their causation, for other factors, such as infections, diet, climate and excessive physical work, have proved themselves inadequate of being the primary cause of these diseases.

## ELIMINATION OF VARIOUS CAUSES

*Infections*—The diseases peculiar to civilized man could not be due primarily to infections, for the same infections affect all races of man, as well as lower animals. There is no evidence suggesting that a specific infection causes any of these diseases in the sense in which typhoid fever and diphtheria are caused by specific bacteria. Infection plays only a secondary role.

*Diet*—It can be said that diet is not a primary factor but that it plays a secondary role.

*Climate*—These diseases cannot be due to altitude, to humidity or to temperature, as they appear wherever civilized man appears. However

it is significant that they are more prevalent in the north temperate zone, where man is noted for being more active

*Physical Overwork*—If physical overwork were the prime factor in causing these diseases, then the consistently hard-working horse should have peptic ulcer, hyperthyroidism or neurocirculatory asthenia

A hereditary predisposition played on by adverse factors in the environment or existing in a normal person under excessive strain in one case may produce hyperthyroidism, in another may pathologically sensitize the adrenal-sympathetic system and in still another may "step up" the brain to the breaking point or so facilitate the digestive mechanism in its activations and its inhibitions as to cause spastic colitis, hyperacidity, peptic ulcer or indigestion. These diseases seem to be largely due to hyperactivity of the group of organs that initiate and continue the transformation of energy. They belong to the diseases of pathologic physiology, bred in man's phylogeny, in which there is a sustained, abnormally high activity of the entire kinetic system. Thus, these mental and emotional states leading up to hyperthyroidism, neurocirculatory asthenia or peptic ulcer may be regarded as the consequence of pathologic activation of the "brain-thyroid-adrenal-sympathetic system"

#### NEUROCIRCULATORY ASTHENIA

During the World War a certain number of men in service at the front became incapacitated on account of a disorder which was called "soldier's heart." These patients exhibited a rapid heart beat, nervousness and fatigue. In the stress of civilian life there are observed many cases of this same disease, which is usually given the name "neurocirculatory asthenia." This disease resembles, and is often mistaken for, mild hyperthyroidism, especially in those cases in which there are a goiter and a moderate increase in the basal metabolic rate. It is a pathologic state of excessive stimulation of the adrenal-sympathetic nervous system due to changes in facilitation within that system itself or to constant thalamic stimulation, and, since other kinds of treatment have failed uniformly, my associates and I followed the results secured by the surgical treatment of hyperthyroidism and sought in selected cases of neurocirculatory asthenia to reduce by surgical measures the activity of the adrenal-sympathetic system.

This condition is most frequently found in persons in a state of worry about finances or environmental conditions grafted on a background of brilliant achievements in school and college.

Since I considered that the adrenal glands constitute the power station, or the brain, of the sympathetic system and that in the presence of neurocirculatory asthenia this power station is too active I tested this conception in certain cases by severing the nerves emerging from the adrenal glands.

My first task was to differentiate neurocirculatory asthenia from a group of diseases which have many symptoms in common with it. I excluded the diseases analogous to it, the mechanism of which involves changes in the patient's fundamental personality, such as psychoneuroses, psychoses and constitutional inferiority, in short, I excluded all cases of patent psychic disease and limited my attack to those cases in which a pathologically excessive activity of the adrenal-sympathetic system was manifested and a classic picture of abnormal stimulation of the sympathetic nervous system was produced.

The theoretic and practical indication for denervation is found in the person whose mental and psychic mechanism acts within a normal range but whose system is under an otherwise uncontrollable stimulation analogous to that which produces hyperthyroidism or that which produces Raynaud's disease.

Neurocirculatory asthenia is more frequently found among women than among men and is essentially a disease of early adult life. The more nearly the symptoms resemble those of hyperthyroidism, the better the operative results. As with hyperthyroidism, the physical type of the patient with this condition is the slender, nonathletic type, a fact which indicates that while the kinetic system is rising the rest of the organism is declining, thus following the pattern of orthogenesis. As has been stated, patients with neurocirculatory asthenia are generally intellectually and emotionally outstanding, just as civilized man is intellectually and emotionally outstanding in comparison with primitive man.

#### PEPTIC ULCER

The seven biologic excitants of the adrenal-sympathetic system are pain, emotion, infection, hemorrhage, asphyxia, thyroid hormone and epinephrine. Pain certainly aggravates a peptic ulcer. Emotion and physical exertion are closely related, both aggravate peptic ulcer, as do equally the toxins of infection. The thyroid hormone my associates and I also believe to be clearly related to peptic ulcer, as we have noted cases of peptic ulcer associated with hyperthyroidism. In these cases thyroidectomy has been followed by cure not only of the hyperthyroidism but of the ulcer.

Accordingly, when there is obstruction at the pylorus it may be assumed that a healed, or at least an inactive, ulcer exists. In this case almost ideal results are secured by a simple gastroenterostomy. When there is an active nonobstructive ulcer in an active, young, high-strung, worrying person, gastroenterostomy is not indicated, because of the tendency to formation of recurrent ulcers. Recurrent ulcers are more resistant to treatment than is the primary ulcer. In the case of a recurrent, intractable ulcer in a young person with a high-strung

worrying temperament, we seek to change the pathologic physiology by denervation of the adrenal glands, otherwise, gastric resection is the operation of choice

#### DIABETES

Cannon has shown that glycosuria accompanies emotion. If the pathologically high stimulation of the pancreas by the highly charged sympathetic system in cases of hyperthyroidism contributes to or causes diabetes, the disturbed carbohydrate metabolism should be abated or cured by thyroidectomy. Dr. Henry J. John found cure or abatement of the diabetes after thyroidectomy in 55 per cent of cases in which diabetes was associated with hyperthyroidism.

#### ESSENTIAL HYPERTENSION AND HYPERTHYROIDISM

Essential hypertension and hyperthyroidism can perhaps best be taken up as a comparative study. Through my observation and study of the histories of patients with these conditions, I have noticed that with each there is a distinct difference in personality and that apparently there is an inherited type of physical characteristics predominant in the hypertensive patients and distinctly different from that observed in the patients with hyperthyroidism. The hypertensive patients are, in the first place, of a heavier build, usually averaging 20 to 30 pounds (9 to 13.5 Kg.) more than patients of the same height with hyperthyroidism. They have larger hearts, larger celiac ganglions, a larger trunk and an especially large chest. They are endowed with tireless energy, and, although both groups of patients have a capacity for large amounts of work, patients predisposed to hypertension have a greater capacity for *sustained* output of energy. The hypertensive person at school tends to be interested in physical work, and he is a leader in organizing teams and clubs. He is usually the student who makes a name for himself in such athletic pursuits as football, boxing and baseball, whereas the person with a hyperactive thyroid is more interested in such activities as debate, creative writing and the more esthetic subjects and displays a definitely higher scholastic ability. With this ability there is associated a more unstable, excitable type of personality, which is often in conflict with the driving ambition generated by the high degree of intelligence. The hypertensive person throughout life is able to do vast amounts of work, but unlike the person with hyperactivity of the thyroid, he is stable and constant, which aids his high intelligence in fitting him for a prominent position in business.

When one sees these two different groups of patients in the clinic, the mental and emotional variations are apparent. The hypertensive patient, who calmly discourses on his symptoms, is rarely alarmed in the least when it is suggested that he should have an operation, often

showing less concern than the surgeon. On the other hand, the patient with hyperthyroidism is so excitable and unstable that the whole hospital must be organized to keep from him the details as to when his operation is scheduled, in order to prevent the development of a thyroid crisis.

*Essential Hypertension*—Barker and Graham<sup>1</sup> claimed that approximately 15 per cent of all adults have hypertension and that 23 per cent of patients who are more than 53 years of age die of hypertension. Ascroft,<sup>2</sup> from a survey in England, says that, after the age of 50, 1 death in 4 is due to arterial hypertension, and he claims further that "whatever the initial cause of raised blood pressure, in 'essential arterial hypertension' the hypertension itself is the dangerous factor and the commonest cause of death."

The racial distribution of hypertension indicates that the highest known incidence of high blood pressure is among those who struggle with the complexity of civilization. Thus, in the aboriginal native whose ceremonies protect him against social struggle, the incidence of hypertension appears to be low. On the other hand, in the urban American Negro, who has been removed for several generations from his protective aboriginal society, the incidence is higher. This seems to be true also of the recently westernized Japanese, who now appear to have a high incidence of hypertension as compared with a presumably similar stock, the calm Chinese, who have not yet been influenced by the pressure of Western civilization.

It is important to determine what levels of blood pressure should be considered hypertensive before any other steps are taken. It is generally considered that in middle-aged or young persons a systolic blood pressure of 140 to 150 mm of mercury and a diastolic blood pressure of 90 to 95 mm is either borderline or indicative of early hypertension. In older patients a systolic pressure of 150 mm is usually accepted as the minimal hypertensive level.

It has been observed that the sympathetic system has an important function in the production and maintenance of high blood pressure. I have already reported that in the course of denervation of the adrenal glands and division of the splanchnic nerves if the sympathetic nerves are manipulated there is a rise in the blood pressure, both systolic and diastolic, sometimes to such a height that it cannot be measured by a manometer, while, on the other hand, if the field is first flooded with procaine hydrochloride there is no rise but rather a dramatic fall in

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1 Barker, N. W., and Graham, R. W. Treatment of Hypertension. *W. Clin. North America* 22:1021 (July) 1939.

2 Ascroft, P. B. Surgical Treatment of Arterial Hypertension. *Lancet* 2:113 (July 15) 1939.

the blood pressure. The adrenal-sympathetic complex is the only tissue in the body the manipulation of which can thus specifically affect the blood pressure.

On the basis of these observations my associates and I resected the celiac ganglions and broke up the sympathetic complex. It was hoped that the operative procedure based on these findings might enable us to reduce the high blood pressure of a patient with essential hypertension to normal on the operating table, and it was felt that, since postganglionic fibers cannot regenerate, there should follow a reduction in the blood pressure.

We have treated hypertension by 535 operations on 314 patients, of which 434 were celiac ganglionectomies on 260 patients. Sixty-one patients were operated on three or more years ago. The average blood pressure of the patients living at the time of this report (55 per cent) was 213 systolic and 130 diastolic on admission to the hospital, at present the average blood pressure is 187 systolic and 116 diastolic. Symptomatic relief has been experienced in 88 per cent of our total series, precordial pain has been relieved in 83 per cent, and 82 per cent of the patients have gone back to work.

Among the patients who left the hospital three or more years ago, 33.3 per cent have died after varying periods. It is generally accepted that approximately 60 per cent of patients with essential hypertension, if not operated on, die from cardiac failure. Of our series of patients on whom celiac ganglionectomies were performed, only 11.8 per cent died from cardiac failure. Also, in our whole group of patients there has not been a single "cardiac death" in the hospital following the operation.

*Hyperthyroidism*—Denervation of the adrenal glands can convert a hyperplastic thyroid into a colloid goiter, thus abating the symptoms, reducing the patient to a normal state and sustaining this normal state. Since denervation can accomplish this, hyperthyroidism is not due to a dysfunction of the thyroid or to a change in the iodine molecule, nor does it originate in the thyroid itself. It is imposed on the thyroid from influences outside the gland and is not due to diet or to changes in the blood.

The curative effect on hyperthyroidism produced by adrenal denervation clearly demonstrates that the hyperthyroidism is definitely related to the brain-adrenal-sympathetic system and does not stand alone as an isolated phenomenon. It is an excessive functional or pathologic stimulation of the entire mechanism of civilized life. The background of civilization and the background of hyperthyroidism are identical, whereas among the wild and the domestic animals, among the primitive races of man and among the drifters, the morons, there is generally neither hyperthyroidism nor civilization.



Through results obtained from our research laboratory my associates and I concluded that nothing but epinephrine can cause the crisis of hyperthyroidism. It followed that if we could sever the connection between the adrenal glands and the organism, not only would this body-wide stimulation be reduced but the activity of the thyroid gland and of the brain would be diminished.

The effects of adrenal denervation in a case of hyperthyroidism may be favorably compared with those of thyroidectomy. After thyroidectomy the patient is at first extremely nervous and difficult to quiet, while after denervation, to the extent that preoperative excitation is avoided, the patient usually is calm and rests well. More sedatives are required after thyroidectomy than after adrenal denervation. After thyroidectomy the pulse rate is usually increased and remains so for several hours, after adrenal denervation the pulse rate gradually drops. Excessive perspiration is noted after thyroidectomy, and little or none occurs after adrenal denervation.

The immediate beneficial results are thus obvious, the remote results should be just as obvious, since the power of the adrenals to excite the thyroid to increased activity is permanently lessened. In our series of cases of hyperthyroidism associated with hyperplasia of the thyroid in which adrenal denervation has been performed, we have seen the entire picture of hyperthyroidism disappear promptly, the basal metabolic rate return to normal and the hyperplasia undergo transformation to the safe colloid state.

#### CONCLUSIONS

The diseases peculiar to civilized man would seem to be due to excessive use of those organs that through their development have distinguished civilized man from primitive man and, in turn, have distinguished primitive man from the domestic and wild animals. The real background of these diseases is the background of the power and personality of man—the brain, adrenal, thyroid, sympathetic nervous system complex, which has evolved to its highest development in civilized man. The principle is analogous to the mechanical effect of putting into an ordinary motor car an engine twice as powerful as the car was designed to handle. If the car were not used there would be no difficulties, but if in addition to having high-powered equipment it were driven excessively, as civilized man is, then complications could be expected. Civilized man has the most highly energized formula of all the animals in the world, and his life in the north temperate zone is such that he is driven at a speed as though life were a race. Consequently, pathologic physiologic change develops which may produce diseases of the coronary arteries, diabetes, peptic ulcer, hyperthyroidism or essential hypertension.

Naturally, the African native with his low energy equipment could not qualify either for civilization or for these diseases of civilized man.

An important part of treatment is clearly prevention. One may hope that some day civilized man will understand the limitations of his equipment, so that by training and education he may adapt the coming generations to the risk of these diseases. When this has developed, there will also evolve better modes of treatment. The present surgical treatment of interference with the sympathetic nervous system's influence on the thyroid gland in conditions of neurocirculatory asthenia, hypertension, hyperthyroidism etc., although as yet with an undetermined effect in some cases is leading the way in this evolution.

# REMOVAL OF LONGITUDINAL SINUS INVOLVED IN TUMORS

WALTER E DANDY, MD

BALTIMORE

There is occasionally presented to the neurosurgeon the problem of dealing with dural meningiomas that have invaded the longitudinal sinus and especially with bilateral dural tumors in which the longitudinal sinus is incorporated in the mass. Unless the affected part of the longitudinal sinus is resected there is no possibility of curing the tumor, and, in most instances, so extensively has the tumor grown to the falx and sinus that even removal of the mass with the full expectation of recurrence is well nigh impossible. When the great size of the longitudinal sinus and the numerous large tributary cortical veins entering it from both sides are considered, it is not difficult to realize that surgeons have hesitated to resect the longitudinal sinus both from fear of producing irreparable harm to such a seemingly all-important venous trunk and from the technical difficulties involved. There has been scant evidence indeed to support the thought that resection of this sinus might be tolerated, particularly in its posterior portion. Many patients with thrombosis of the longitudinal sinus have come to necropsy. But in the case of such a patient there is frequently an acute inflammatory basis, and many of the contiguous cerebral veins are also included in the process. Moreover, in many an acute septicemia coexists. It is doubtful whether experimental evidence would be pertinent, except perhaps in monkeys. In dogs there is only one cluster of cerebral veins on either side that enters the sinus, whereas in man there are many.

It is of course, clear that in dealing with bilateral tumors and frequently even with unilateral dural tumors the longitudinal sinus is frequently occluded by the tumor either by compression or by direct invasion, so that removal of a section of the longitudinal sinus really adds little or nothing to the demand for collateral venous circulation. In these cases the venous obstruction has doubtless been gradually progressive, and because of this there has been time for the collateral circulation to develop. This condition was true in both of my cases in which the longitudinal sinus was resected posterior to the rolandic vein and doubtless it was also true in nearly all of the cases reported in the literature. Whether a patent sinus could be similarly resected can only be conjectured, there is no evidence from the literature to support or deny such a claim.

Gradually a small number of cases of resection of the longitudinal sinus in the course of tumor extirpations have been assembled from the literature. Kenyon (1915) reported the first case in which the longitudinal sinus was doubly ligated in the frontal region, the ligatures being  $2\frac{1}{2}$  inches (6.3 cm) apart. Rand (1923) was apparently the first deliberately to resect about 10 cm of the sinus with a large bilateral dural meningioma with massive hyperostosis over it. The resected sinus was well in front of the rolandic vein. The patient made a splendid recovery with no loss of motor function, and a note from Dr. Rand on March 19, 1940, stated that the patient is well eighteen years later, an occasional epileptic attack being the only residual disturbance. In 1926 Towne removed a similar tumor weighing 428 Gm and a section of the longitudinal sinus (length not stated), but his patient died two months later. The longitudinal sinus was filled with tumor.

David, Bissery and Brun (1935) reported a case in which operation was done by Vincent of Paris, France. A bilateral tumor—12 Gm on the left and 18 Gm on the right—was removed with 5 or 6 cm of longitudinal sinus just in front of the rolandic vein. The result was excellent, with no motor loss. No note was made of the patency or occlusion of the longitudinal sinus. Horrax has successfully removed sections of the longitudinal sinus in 2 cases, 1 (1931) included in Cushing's book on meningiomas (6 cm of sinus in front of the rolandic vein was resected) and another, reported by Maltby (1939), in which 4 cm of the sinus posterior to the rolandic vein was excised. The patients in both cases made excellent recoveries, with slight but gradually diminishing spasticity of the extremity. In Horrax' second case resection was done in a single operation, doubtless because his earlier experience had given him a greater sense of security concerning removal of a section of longitudinal sinus. In all the preceding cases the sinus had been resected after recurrence or in stages for tumors of excessive size and vascularity. In Horrax' second case (Maltby) a prolongation of the tumor was drawn out of and doubtless occluded the longitudinal sinus. Rowe (1939) reported another splendid result, with a large bilateral dural tumor with hyperostosis, together with which 6 cm of the longitudinal sinus was resected. A letter from Dr. Rowe stated that he has since been unable to locate the patient and that the patency or occlusion of the sinus was not investigated.

Two remarkable cases (Davidoff [1937] and Tonniss [1935]) complete the series of cases of resection of the longitudinal sinus that I have been able to assemble from the literature—a total therefore, of 9 (in Kenyon's case ligation, not resection was done). The operation in all except Towne's case was successful, without any disturbances attributable to resection of the sinus, and Towne's patient lived over two months. Most of these patients had some degree of temporary

spasticity of the lower extremities after operation, but this was clearly due to trauma of the motor cortex incident to extirpation of the growth and not to any effects of removal of the longitudinal sinus.

Davidoff's case and also that of Tonnus give evidence of the very highest surgical skill, as indeed do all the others, for such operations are no mean feats. Davidoff's tumor, removed in three stages, weighed 835 Gm and was perhaps the largest cranial tumor to have been successfully removed. The hyperostosis and contained tumor weighed 270 Gm, and the intracranial portion, 565 Gm.<sup>1</sup> The length of sinus removed is not stated. A letter from Dr. Davidoff (Jan. 22, 1940) states that, although the patient has some slight spasticity on the right and a slightly hesitant speech, she is quite well and does her own housework.

Tonnus removed not only a section of the longitudinal sinus (length not stated) but part of one transverse sinus and the tentorium, through which the tumor had penetrated into the posterior cranial fossa. And his patient recovered with no defects except homonymous hemianopia.

To the aforementioned group of cases 4 of my own are added. In 2, resection was done in the anteriormost part of the sinus, and in 2, posterior to the rolandic vein. In 2 of the cases the sinus was excised when the tumor had recurred, and in 2 the sinus was removed at the first operation, when the tumor was known to be bilateral.

#### REPORT OF CASES

CASE 1—C. W. L., a white man aged 49, was admitted to the hospital because of headache and a "change of disposition." A cerebral injection of air was performed May 7, 1927. This showed a tumor in the left frontal lobe. An exploration was made May 8, and a small dural tumor, weighing 27 Gm, was removed from the anterior portion of the falx. The tumor was thought to be a dural meningioma. The patient made a complete recovery, and his headache and mental symptoms entirely disappeared.

Four months later he reentered the hospital because his original symptoms had returned. The wound was reopened, and a recurrent tumor weighing 206 Gm was shelled out with the finger. It was realized that this could not be a permanent cure, and two and one-half weeks later (September 20) the wound was reopened and the bone removed over the longitudinal sinus and to some distance on the right side. There were no veins entering the longitudinal sinus on the right side. Clamps were placed across the longitudinal sinus anteriorly, and the sinus was divided. The incision was carried through the longitudinal sinus, and the inferior longitudinal sinus was clipped and divided. The longitudinal sinus was then divided and transfixed even with the posterior margin of the bony defect, and the entire intervening part of the longitudinal sinus and the falx were removed. The remaining ends of the longitudinal sinus were then transfixed with medium silk. The amount of longitudinal sinus removed was 8 cm, this was well in front of the rolandic vein, the posterior ligature in the sinus being about 4 cm anterior to the rolandic vein (fig. 1).

The patient had no after-effects from ligation of the sinus. He recovered completely but returned again seven months later because of recurrence, which was evident from the protrusion at the site of the removal of bone. There was such an extensive return of the tumor that no attempt was made to remove it. The patient died three months later, June 27, 1928.

Autopsy showed massive recurrence of the tumor. No note was made concerning thrombosis of the remaining part of the longitudinal sinus. It was noted that 3 cm. of the longitudinal sinus remained anterior to the ligature in the longitudinal sinus.

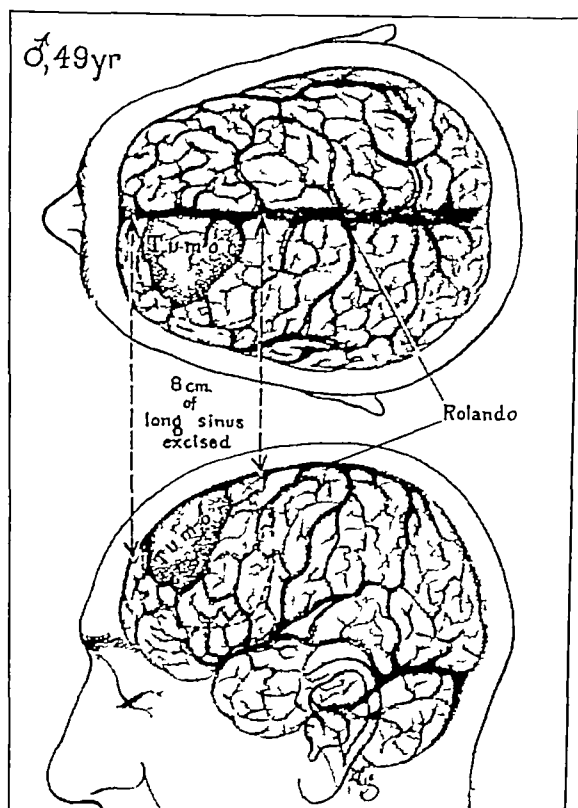


Fig 1 (case 1)—Sketch to show the position of the tumor and the relative amount of longitudinal sinus removed anterior to the fissure of Rolando

CASE 2—F R, a white woman aged 40, had observed a swelling of the forehead for the past twenty-three years, it had been steadily progressing (fig 2). There had been headache and pain over both frontal regions for the past two years and exophthalmos of the right eye over the same period, this, too, had been steadily progressing. Roentgenograms showed tremendous hyperostosis of the frontal bones (fig 3).

Operation—On Nov. 21, 1936, a large sweeping curved incision was made across the frontal region, just under the hair line, it was directed posteriorly and extended from one temporal region to the other. A flap of galea and skin was

thrown forward to the supraorbital ridges. The tumor had eroded through the bone on the right side over a considerable area, but the surface was intact. The bone was so thick that several burr openings were made, and the intervening



Fig 2 (case 2)—Preoperative and postoperative photographs of the patient. The tumor was a bilateral dural endothelioma with tremendous hyperostosis. The tumor had broken through the roof of the orbit on the right side. In the postoperative photograph the patient has concealed the marked frontal depression with her hair.

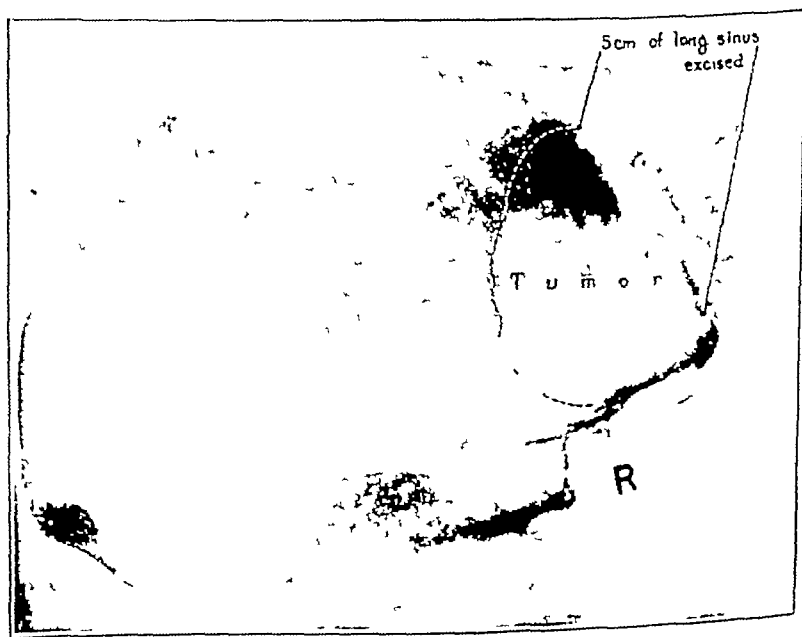


Fig 3 (case 2)—Roentgenogram showing tremendous hyperostosis over a bilateral dural tumor.

bone was cut with large biting forceps. When the bone was turned back and broken across at the supraorbital region the tumor came out with it. It was a large bilateral dural growth (fig 4). The sinus tore across at the posterior margin of the bone, but it bled very little. The mass in the orbit had broken

off from the main growth and was shelled out separately. Several veins crossing from the anterior lobe to the longitudinal sinus were coagulated with the electrocautery. The tumor mass with the overlying bone weighed 296 Gm.

The patient made an uneventful recovery and has been well to date (March 10, 1940). She is constantly employed at full time (fig 2).

The length of sinus removed was about 8 cm.

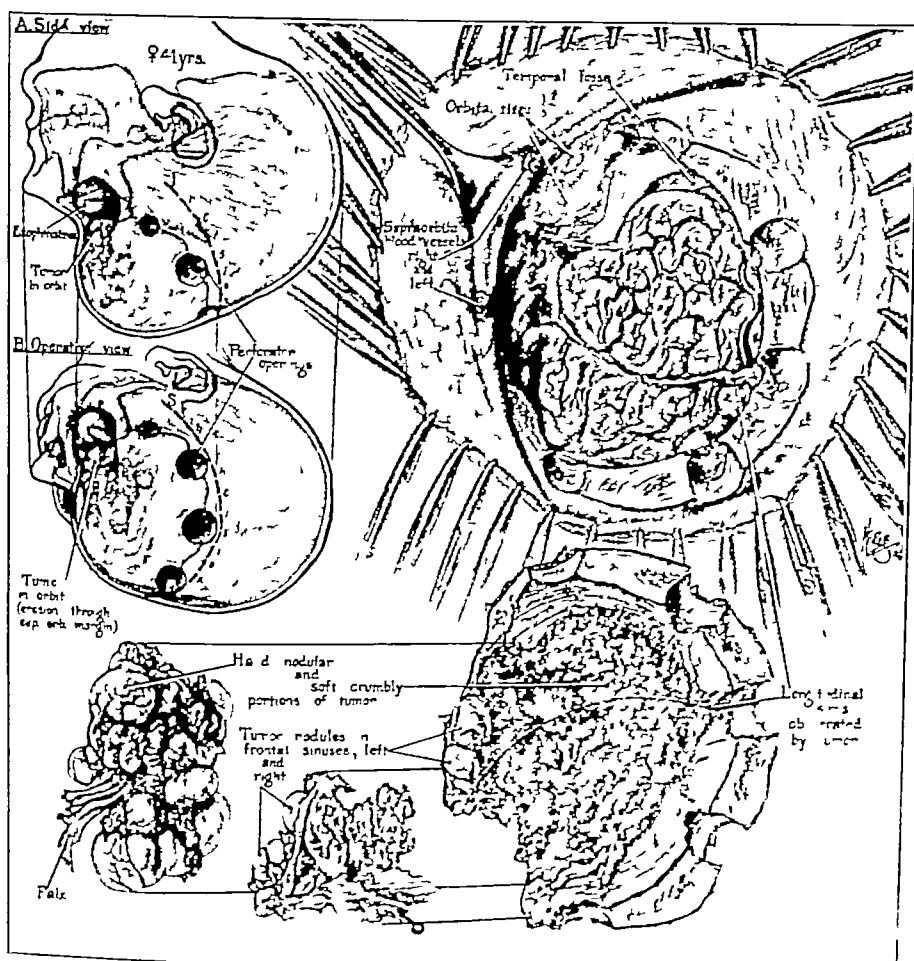


Fig 4 (case 2) —Operative sketch showing the tumor removed and the amount of longitudinal sinus resected.

CASE 3—J W, a man 22 years of age consulted me May 21 1939, because of a prominent swelling over the vertex of the skull. He had had headaches for three or four years, and for the past five months these had become more persistent and more severe, occurring almost daily and lasting from a few minutes to a few hours, they were bilateral and biparietal. The lump on the head was steadily increasing but was not tender (fig 5). His work in college had gradually declined and during the past year he had barely made passing grade. Concern



tration was difficult, his memory was poor, and there had been some difficulty in getting out words and phrases, although he knew them well. On some occasions there had been transitory attacks of blurred vision. On a few occasions he had had cramps in the right leg but not a convulsion.

Neurologic examination showed slight but definite papilledema, with fulness and tortuosity of the retinal veins. The grip of the right hand was slightly weaker than that of the left. During the examination he had a cramp which drew up the right leg severely, and it was very painful. There was slight hypoesthesia in the right arm and leg, the station and gait were not affected. The patient's speech was halting, reading was stumbling but correctly done, but it seemed difficult to get the context of what he was reading. The Wassermann reaction of the blood was negative. Roentgen examination showed marked hyperostosis at



Fig 5 (case 3) —Photograph of the patient, showing marked hyperostosis in the parietal region

the vertex, about equal on both sides of the midline (fig 6). The protrusion was about 1 inch (2.5 cm) above the normal level of the scalp, it was diffuse and even.

**Operation**—On May 23 a long midline incision was made over the tumor and extending well beyond it anteriorly and posteriorly. The galea and skin were then retracted, this exposed the hyperostosis, which was not very vascular. Several burr openings were made in a circle just beyond the hyperostosis, where the bone was nearly normal. With the Gigli saw these openings were connected, and the mass of bone was lifted off the dura and longitudinal sinus. As the bone was being elevated, the tumor could be seen projecting into a deep concavity in the inferior surface of the bone, it was firmly attached to it. By gradually elevating the bone flap and inserting the finger beneath it the tumor was stripped from the concavity in the bone (fig 7). There was very little bleeding from the exposed dura and tumor, application of the electrocautery controlled this. The tumor in the bone was about 2 inches (5 cm) long and 1¼ inches (3.1 cm) wide. The

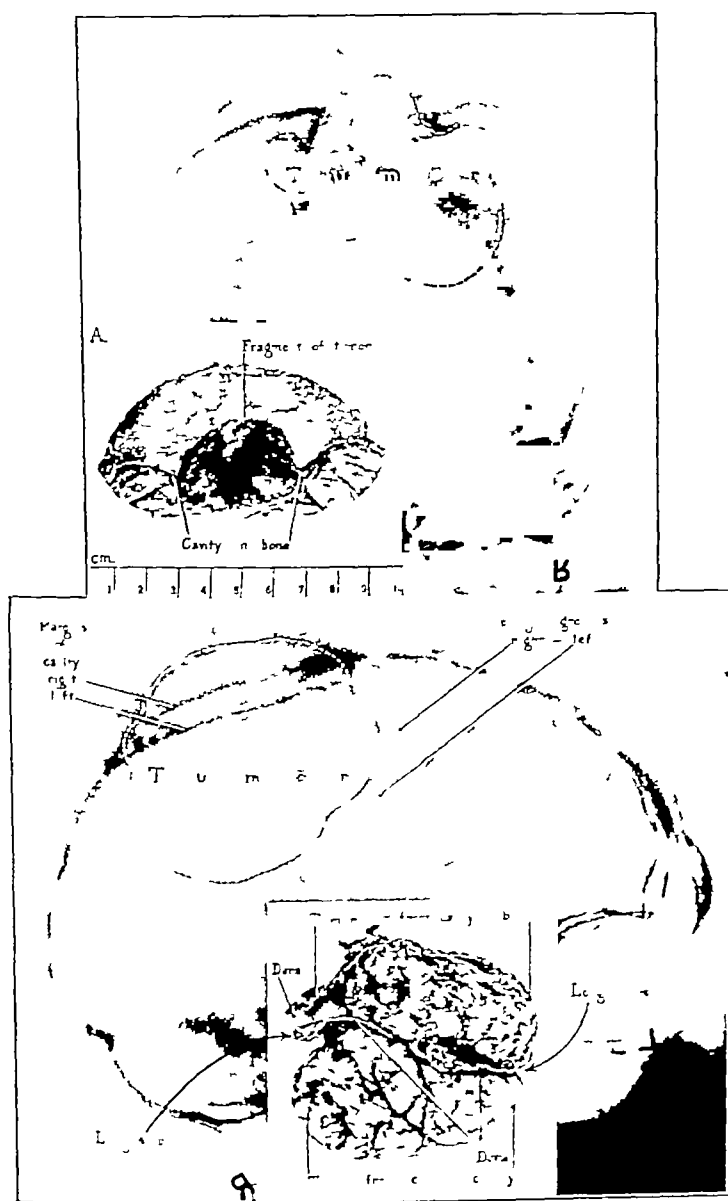


Fig 6 (case 3) —Lateral and anteroposterior roentgenograms of the skull. The marked hyperostosis is shown, and the relative size and position of the tumor are indicated by the dotted lines. The inset in the anteroposterior view shows the section of bone removed with a large piece of the tumor in the excavation on the inferior surface. The inset in the lateral view is a photograph of the tumor and shows the longitudinal sinus, which had been completely obliterated by the tumor.

tumor was entirely on the left side of the longitudinal sinus, which was pushed in a curve to the right. The wound was closed without drainage.

The weight of the bone was 159.1 Gm.

The second stage operation was performed on June 3, ten days after the first operation. The wound was reopened, there was some necrosis on the surface of

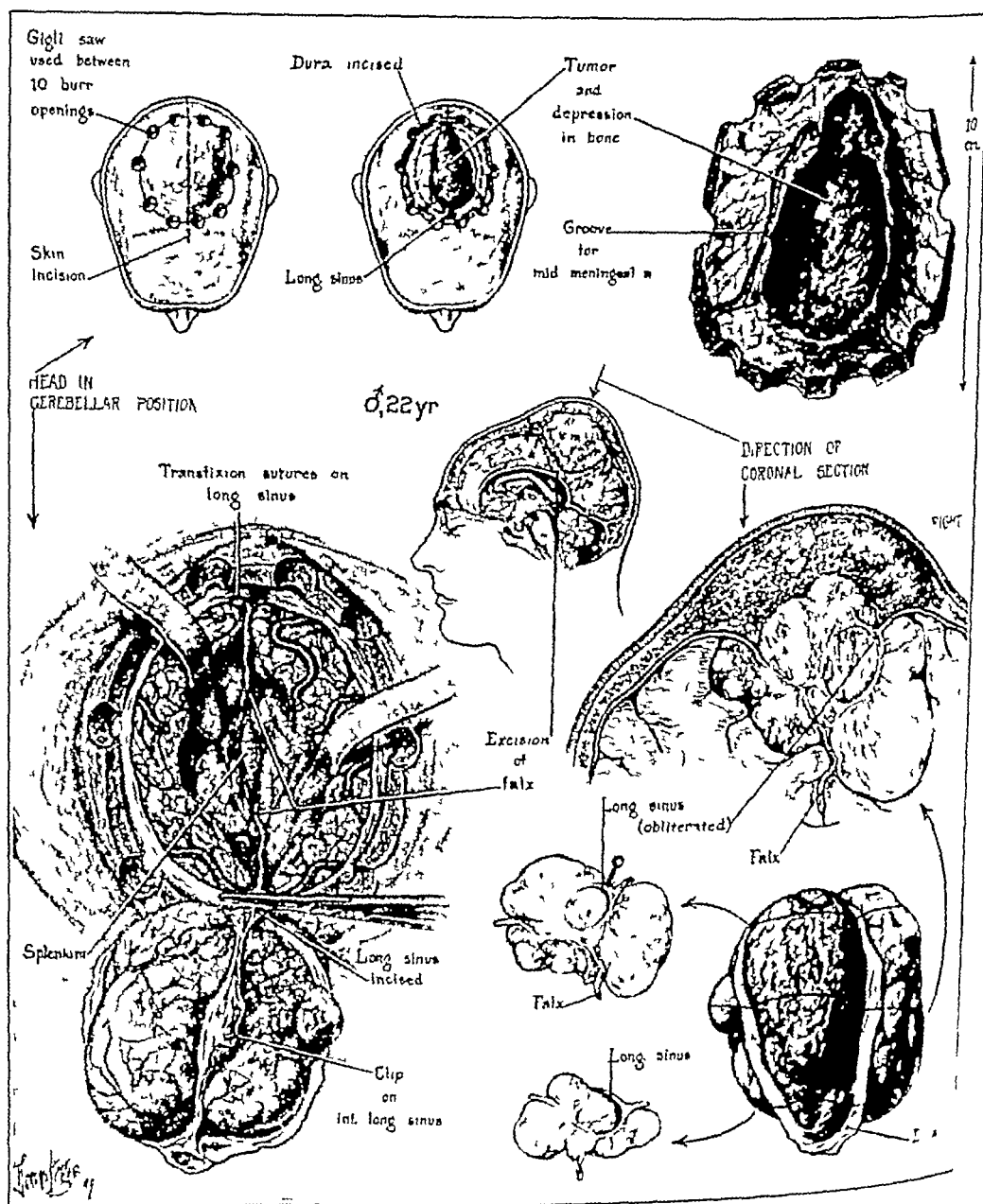


Fig 7 (case 3) —Operative sketch showing the bone removed, the excavation of the hyperostosed bone, the position and character of the tumor and the effect on the longitudinal sinus. The operative view of the removal of the tumor and the longitudinal sinus is shown in the larger sketch on the left.

the exposed tumor. The dura was first opened in a semicircle on the right, the termini being at the border of the longitudinal sinus. The tumor was then pushing the cerebral hemisphere to the right. It was a large, hard growth and

clearly a dural meningioma. It extended deeply along the falx. The dura was then opened on the left side in a similar fashion, and the incision extended to the longitudinal sinus. The longitudinal sinus was then doubly clamped at both ends and just at the margins of the large defect in the skull. The sinus was then cut between the clamps, and the ends were transfixed with sutures of medium silk (fig 7). Several veins entering the longitudinal sinus from the hemispheres

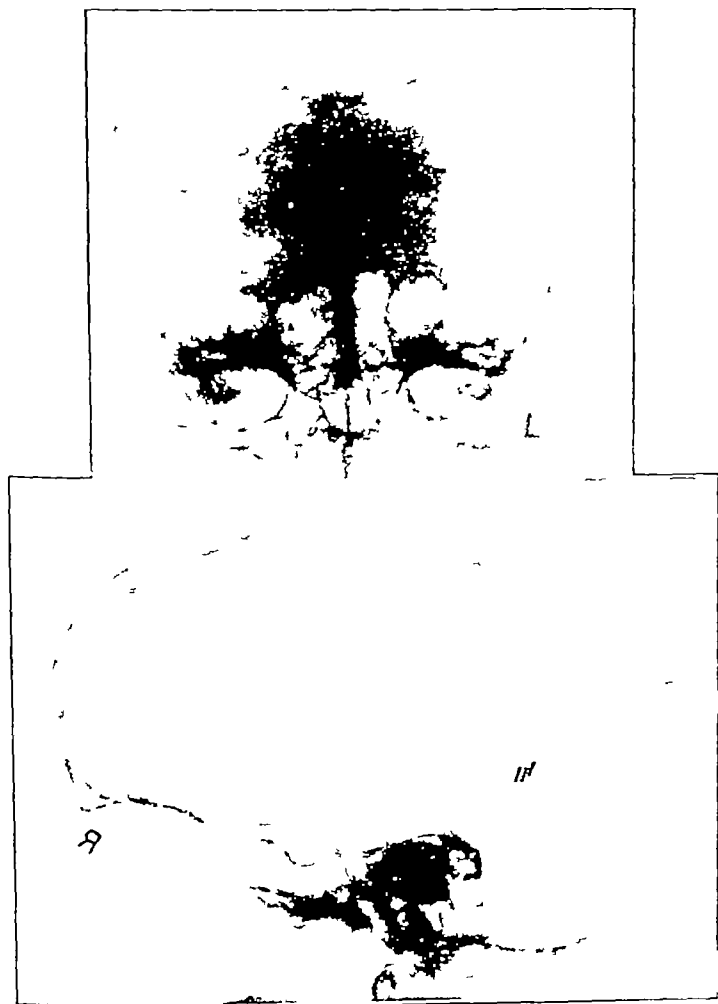


Fig 8 (case 3) —Postoperative roentgenograms showing the amount of bone removed and the position of the silver clips placed on the inferior longitudinal sinus near its entrance into the great vein of Galen.

were thrombosed with the electrocautery and divided. These veins included the rolandic veins on both sides. About eight veins were thrombosed on the two sides, all of them were very tortuous. The falx was then divided through its entire length, including the inferior longitudinal sinus at both ends. The clips shown in the roentgenograms were on the posterior part of the longitudinal sinus (fig 8). After the falx had been cut through at both ends the tumor was gently

shelled away from both hemispheres, it protruded far out on both sides, undermining the hemispheres, but much more on the left. On the right side it was necessary to cut away a small slice of the attached leg center to the depth of about 2 cm and about 1 cm in thickness. This was necessary because the tumor was adherent to the brain at this point. The tumor was bulging far out on both sides in the depths of the brain, but it was easily separated from it, with very slight trauma, the bulge was greater to the left. Little bleeding attended extirpation of this mass. A piece of fascia lata was removed from the right leg and carefully sutured to the dural margins, completely covering the entire dural defect. The wound was closed without drainage.

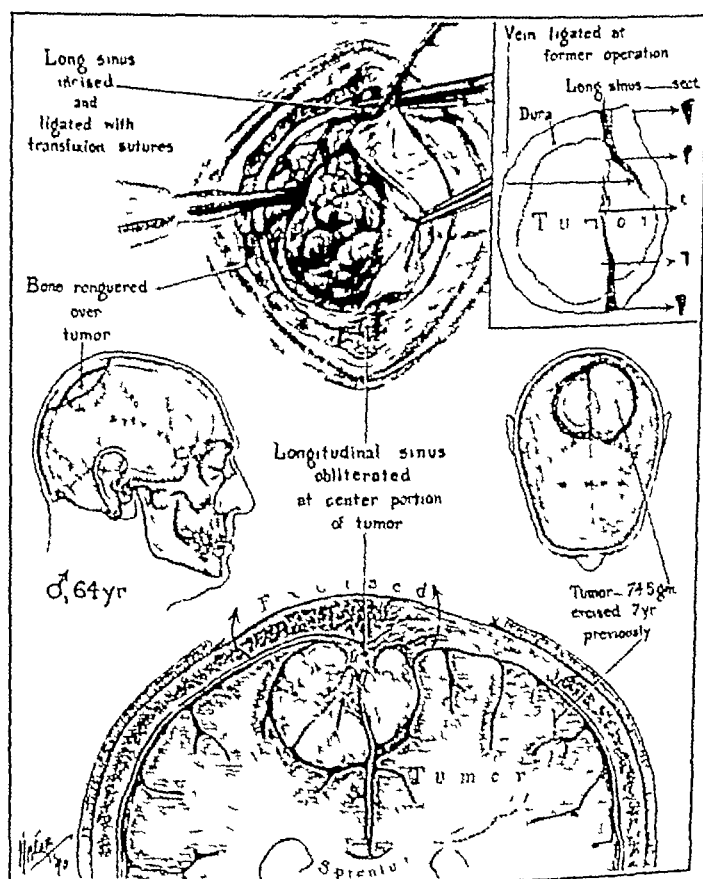


Fig 9 (case 4) —Operative sketch of removal of the tumor. It was a bilateral dural endothelioma over which there was slight hyperostosis. The position and relative length of the resected longitudinal sinus and the relative size of the tumor are indicated. The longitudinal sinus had been obliterated by the tumor for a distance of 3 cm at the center of the tumor.

The tumor weighed 170.3 Gm. The total weight of the bony growth and the bilateral tumor was 329.4 Gm.

The patient was conscious soon after the operation and moved both legs and arms freely. Later in the afternoon he was unable to move either leg. The first movement in the left leg began six days later, and slight movement in the right leg began on the following day. There was also diminished sensation in the legs during this period, but on the day before the motor function began to return he noticed increased feeling in both legs.

Microscopic section of the bone showed typical dural meningioma cells, and sections of the tumor showed typical dural meningioma with whorls of fibrous tissue. The longitudinal sinus was totally occluded over about three-fourths of the removed portion. The length of the longitudinal sinus was determined at the time of operation and was 12.5 cm.

*Subsequent Course*—The patient's motor function steadily improved. He left the hospital June 18, thirteen days after the last operation. At that time the power was not sufficient to support him, but during the summer months he improved rapidly, and when I last saw him (Jan. 20, 1940) he was walking with very slight disturbance of gait, the two legs were equally good. He had just returned to college for the second semester, he was keen and alert and said he felt that he had completely returned to his normal mental state. The wound was soft and sunken, and there was no evidence of recurrence.

CASE 4—L. P., a white man aged 56, was operated on May 6, 1933. A dural endothelioma was removed from the falx on the left side, in the postrolandic area. The symptoms of the tumor were convulsions beginning in the right leg and weakness of the right leg. The tumor removed at this time weighed 63 Gm.

Four and one-half years later (Jan. 7, 1938) a recurrent tumor was removed from the same side, it weighed 12 Gm. The patient had slight motor disturbance in the right leg following this operation, but he walked well.

On Jan. 17, 1940, he returned because of a similar weakness in the left leg. It was clear that he had a similar tumor on the right side of the falx. He was again operated on (January 23), and a tumor weighing 35 Gm was removed from the right side, together with the intervening longitudinal sinus and falx (fig. 9). There was no recurrence on the left side. The length of resected longitudinal sinus was 6.5 cm and extended backward from a point about 2 cm posterior to the rolandic vein. Five centimeters of this had been completely obliterated by the tumor, which had grown directly through it.

The patient had no increase in motor weakness following removal of the sinus and tumor. On the day after the operation his general condition was as good as before the operation. There were no noticeable effects from extirpation of the longitudinal sinus, and none could be expected, because the sinus had been completely obliterated by the tumor. He left the hospital two weeks later.

The postoperative course was uneventful.

#### SUMMARY

In none of the 4 cases was there any motor, sensory or other loss that could be attributed to removal of the longitudinal sinus.

The length of the longitudinal sinus removed was 5 cm and 8 cm respectively, in the 2 cases in which resection was anterior to the rolandic vein and 6.5 cm and 10 cm, respectively, in the 2 cases in which resection was posterior to the rolandic vein.

In 3 cases and probably in the fourth the longitudinal sinus was already obliterated over much of the excised portion owing to compression or actual invasion by the tumor. There is as yet no available evidence by which it can be known whether the longitudinal sinus can be removed in part before gradually progressive occlusion has occurred.

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## SOME ETIOLOGIC AND PATHOLOGIC FACTORS IN CANCER OF THE LARGE BOWEL

VERNON C. DAVID, M.D.

Chairman, Department of Surgery, Rush Medical College  
CHICAGO

The object of this paper is to call attention to the frequency of occurrence and the histologic structure of supposedly benign polypoid growths originating in the large bowel and to present some evidence of their relation to cancer of the large bowel. Studies of these various factors have been made on material covering 200 resected cancers of the large bowel in over 300 patients on whom I have personally operated for that lesion and on 100 additional specimens of supposedly benign polyps of the colon and rectum.

The incidence of mucous polyps of the large bowel varies considerably, depending on whether they are discovered as a result of examination of patients complaining of significant symptoms or whether their frequency is noted as a result of routine postmortem examination. Even the latter approach is not ideal unless a meticulous examination of the entire area of the large bowel is carried out, for these polyps in many instances are small and hidden between the folds of mucosa. Fortunately, such a thoroughgoing search was made in 1,800 consecutive autopsies by Feyrter<sup>1</sup> in 1929. He observed 1,017 polyps in 1,110 of the colons examined. In discussing such observations it is important to attempt to designate which of the lesions are true tumors and which are simple hyperplasias on a senile or an inflammatory basis. This is extremely difficult to do, as many of these lesions blend one into the other, with minor histologic differences. Several gross and histologic divisions of these lesions can be made, however, and at the outset it would seem advisable to make them.

One of the most common deviations from the normal in the mucosa of the colon is the occurrence of millet seed-sized flat elevations, which are usually multiple and occur mostly in old persons in whom they may be but another example of the hyperplasias occurring on a senile basis in other parts of the body—for example the skin. They also occur as an inflammatory lesion, for instance on the mucosa or a colostomy stoma. They are also commonly seen as multiple lesions in the mucosa of the bowel 3 to 6 inches (7.6 to 15.2 cm.) above or below an ulcerating

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<sup>1</sup> Feyrter, F. Zur Lehre von der Polypenbildung im menschlichen Darm.  
Wien med Wchnschr 79:338-342 (March 9) 1929.



carcinoma of the bowel. Because of this position contiguous to a carcinoma it has been argued that the carcinoma may have sprung from such areas showing a tendency to growth. It could be stated equally well that they are inflammatory in origin and consist of inflammatory hyperplasia of the mucosa resulting from a reaction to the infection and irritation from broken-down tumor tissue in their immediate vicinity. The histologic structure of these minute lesions shows them in the main to be simple hyperplasias with inflammation or lymphatic hyperplasia of

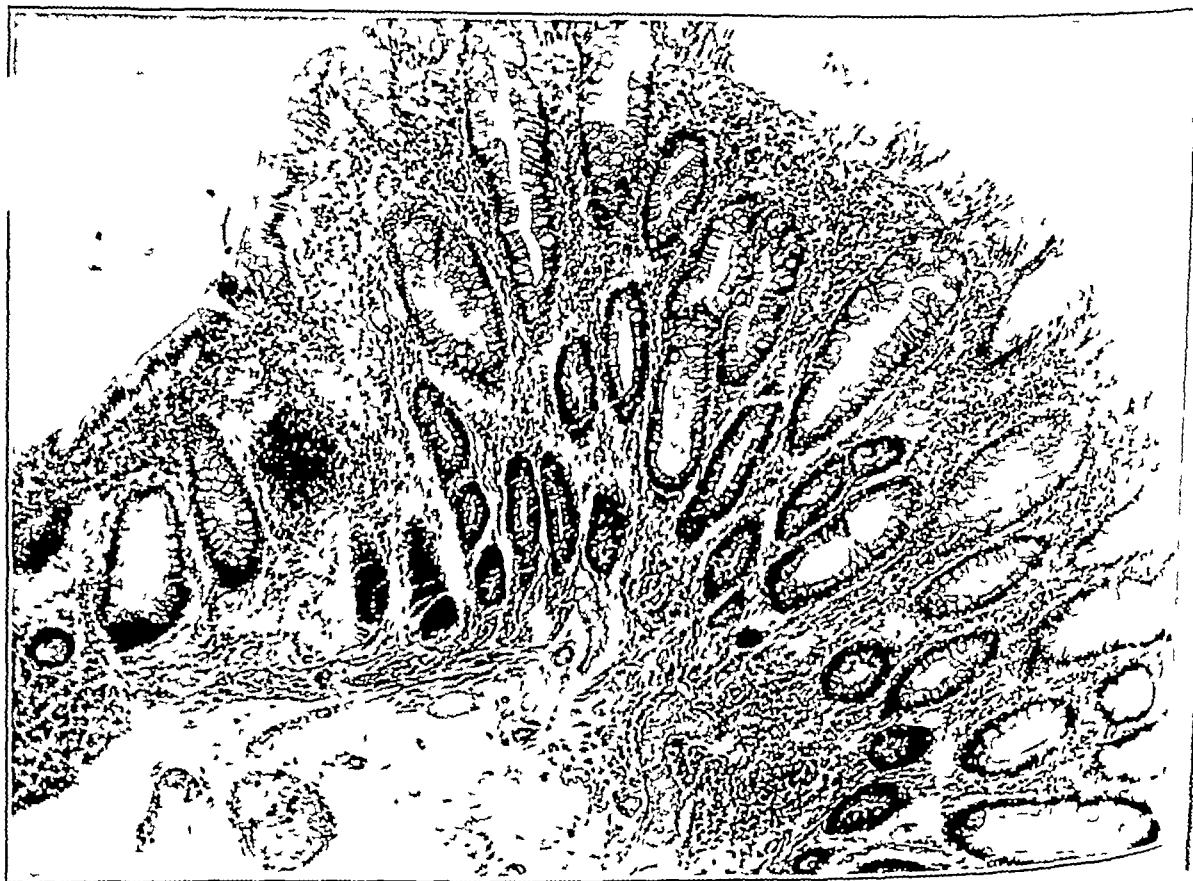


Fig 1—Two millimeter elevation of the mucosa near a carcinoma of the rectum, showing hyperplasia of the epithelium and inflammatory exudate between the tubules. Similar lesions appear on colostomy stomas.

the submucosa. The glandular structures of the mucosa are enlarged. The tubules of the mucosa are increased in length and have a slight tendency to branch, but the staining properties of the cells are those of the surrounding mucosa, and the relation of the cells of the tubules to the basement membrane is everywhere preserved (fig 1). However, in exceptional instances the cells of the lesions may take on deeper staining properties, the tubules may be branching and the general appearance of the lesion may closely resemble that of larger polyps which are almost certainly tumor and not simple hyperplasia.

The lesion in figure 2 appeared on the exposed mucosa of a colostomy stoma several weeks after the colostomy was performed. In this group of small elevations of the intestinal mucosa it is not easy to differentiate hyperplasia, senile or inflammatory, and tumor growth. In Feyrter's series, 762 of the lesions found were of this type.

The next type of polyp frequently seen is the adenomatous polyp. This lesion varies in size from that of a pea to that of a large cherry and



Fig 2—Hyperplastic nodule which developed on the mucosa of a colostomy opening. Note the branching tubules which resemble adenoma.

may have a sessile attachment, especially when small, or a pedicle when larger, due to stretching and pulling on its attachment by the peristaltic action of the bowel in its attempt to propel it along with the rest of the intestinal contents. The lesion may be transparent and of the same color as the mucosa in which instance its histologic structure is more akin to the normal mucosa of the bowel in that the epithelial covering of the polyp is more like a hyperplasia, the cells having but little differ-

ent staining properties from normal epithelium and the body of the polyp containing sparse epithelial elements, many of which are cystic. The stroma surrounding these cystic dilatations of the tubules may have considerable round cell infiltration or inflammatory exudate. This type of polyp is the one most commonly found in children and may have a pedicle of normal mucosa 2 to 3 inches (5 to 7.5 cm) long. This same type of lesion is found in adults and has all the indications of being a benign lesion, with little tendency to rapidity of growth or loss of differentiation of the epithelial elements (fig 3).

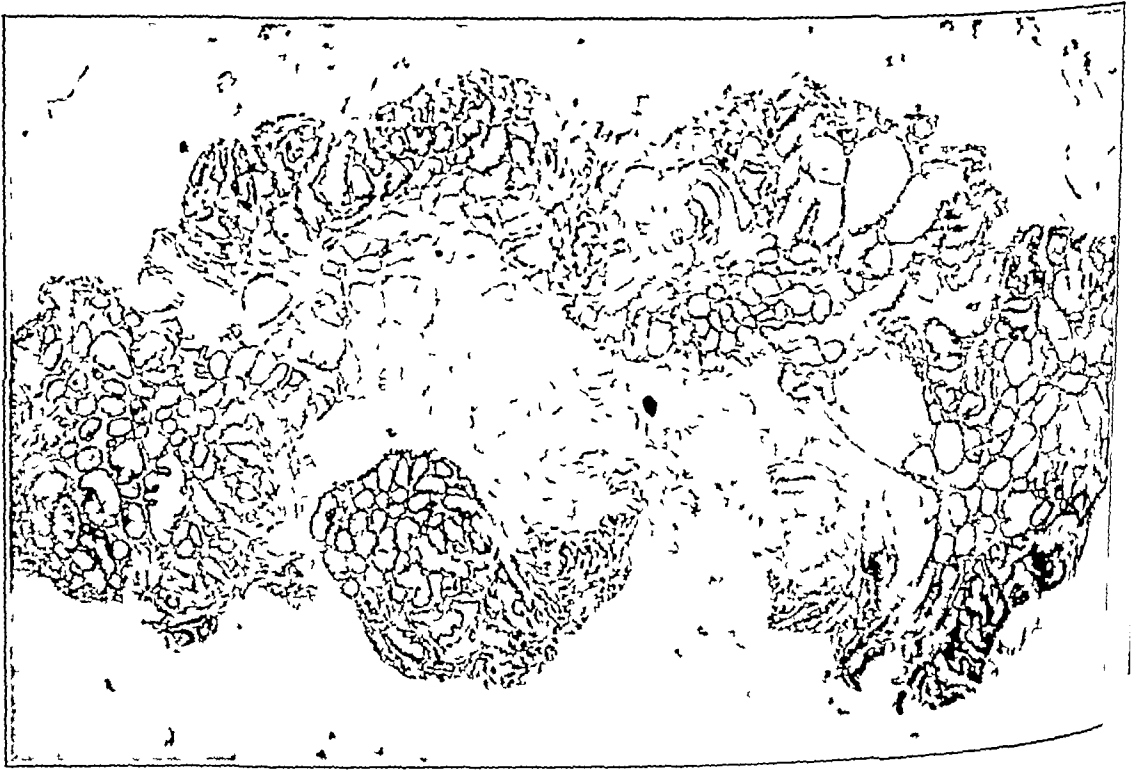


Fig 3—Pedunculated adenoma of the rectum. The structure is simple, but there is definite tumor formation.

Almost insensibly changing in structure are other polyps of this adenomatous group which have every evidence of a growth or tumor change in their epithelium (fig 4, top). The color of these polyps is plum or cherry. The staining properties of the cells are strikingly different in that the protoplasm stains more deeply, as does the nuclear substance, in which mitotic figures are not common. The layers of cells in the tubules are increased in number. At the base of the adenoma the structure of the tubules is more nearly normal than at the periphery of the lesion, where branching of the tubules and cuplike enlargement of the glands take place, and a beginning loss of order of the epithelium in relation to the connective tissue pedicle of the polyp is observed.

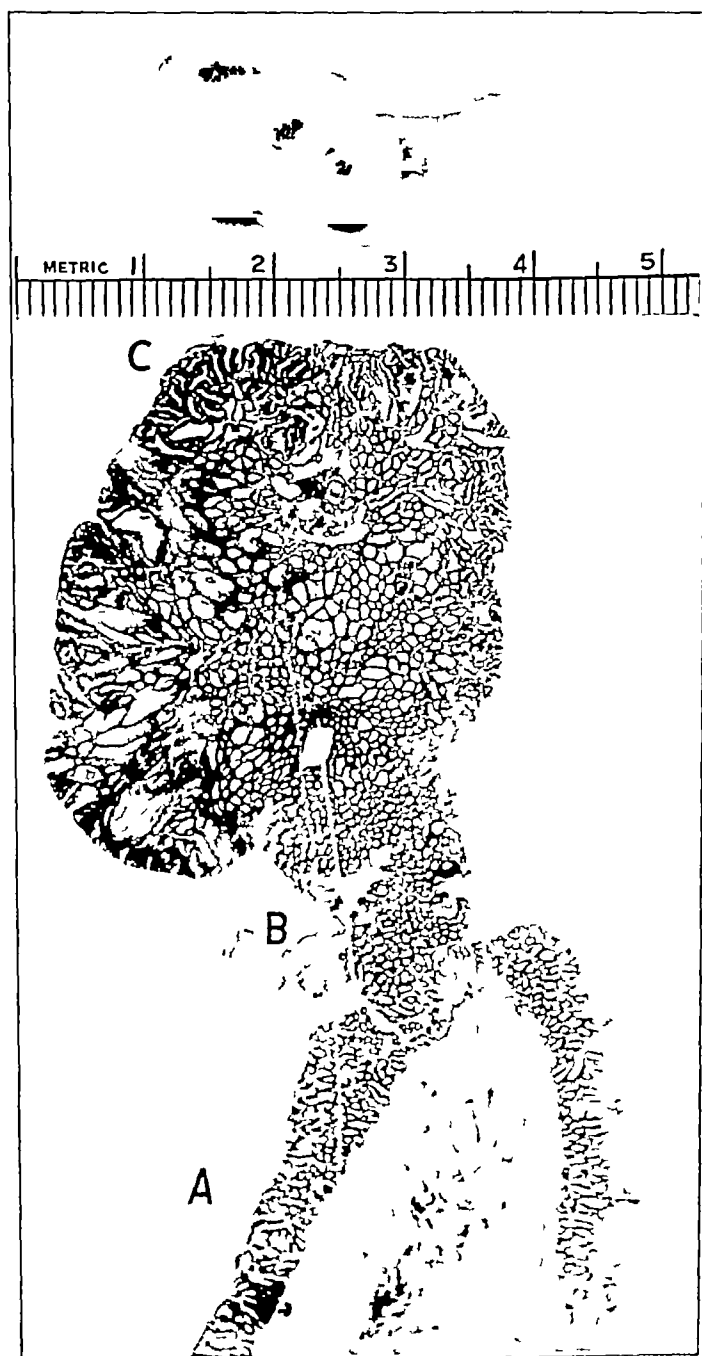


Fig. 4—Top, pedunculated adenoma of the colon. There is a pedicle of normal mucosa. The tumor is lobulated. Bottom, pedunculated adenoma of the colon. A, normal intestinal mucosa. B, pedicle of normal mucosa. C, brush border in the periphery of the tumor showing loss of orderly arrangement of deep, a, stem cells and nuclei.

In these lesions, however, the relation of the epithelial elements to the basement membrane is everywhere preserved. These polyps may become large, with a cauliflower surface, and contain branching stalks of connective tissue (fig 4, bottom). It is easy to see that in this type of adenoma the mucosa has taken on real growth propensities and that one is dealing with a tumor benign in structure.

Westhues<sup>2</sup> has well described, and, I believe, with reason, a still more advanced tissue change in these adenomas, which brings their structure closer to that of a carcinoma. In these adenomas nearly all

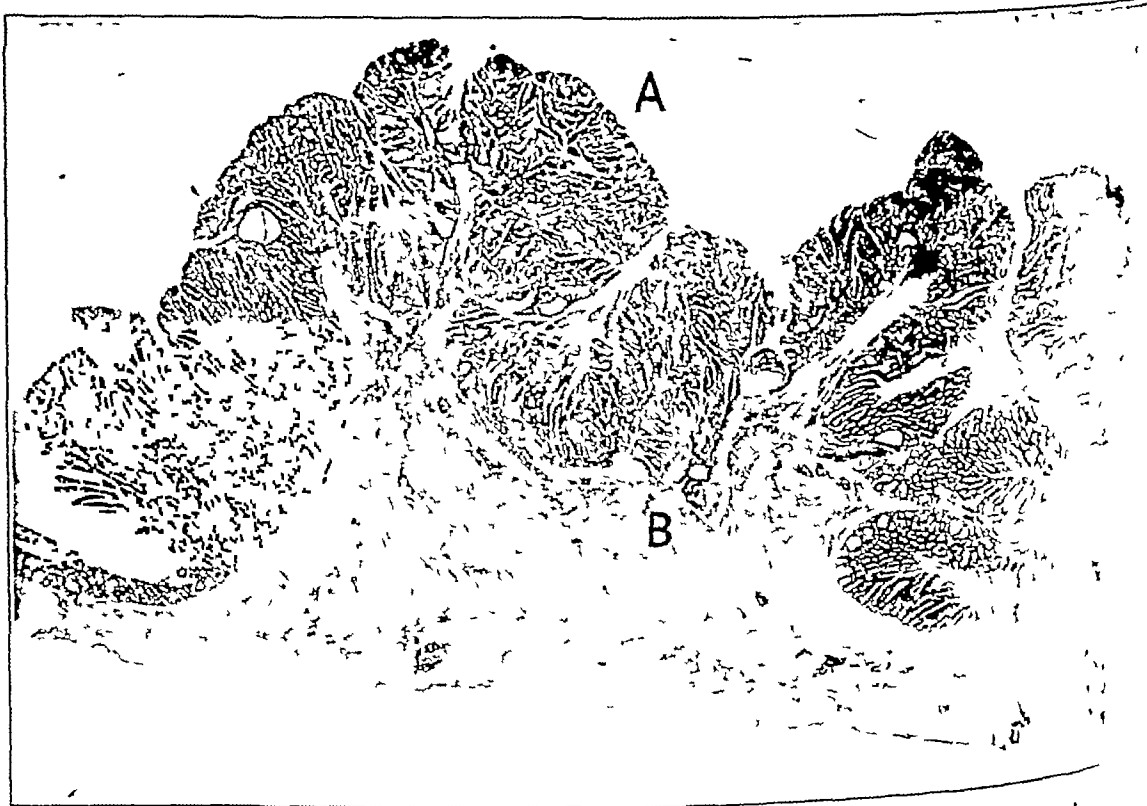


Fig 5—Flat adenoma of the sigmoid flexure of the colon, with complicated epithelial structure (A) and loss of muscularis mucosa in some areas (B)

order in the epithelial structure is lost. The branching, elongated tubules with cuplike outgrowths, the cells of which are many layered and deeply staining, have lost a definite relation to the basement membrane. The muscularis mucosa is absent in many places rather than broken through, and the connective tissue pedicle is sparse or absent in many places. At the base of the lesion the glandular tubules are distorted and pushed apart (fig 5). It is but a step from this structure to actual infiltration and invasion, which, in my opinion, must still

<sup>2</sup> Westhues, H. *Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms*, Leipzig: Georg Thieme, 1934.

the criterion for a diagnosis of malignant disease. It becomes increasingly apparent how difficult it is for a diagnosis to be made from a small piece of tissue taken for biopsy. The general structure of the epithelial elements may be determined and the growth tendency appreciated, but in this type of lesion the gross appearance and physical characteristics of the lesion should be correlated with the histologic structure, for the reason that any evidence of ulceration or induration of the lesion speaks volumes in favor of malignant degeneration.

Another gross division of benign polypoid tumors of the large bowel is that of papillomas or villous tumors. The tumors vary in size from arborescent stalks with the gross appearance of waving, delicate vegetation to large, flatly attached soft tumors the size of an adult fist, almost

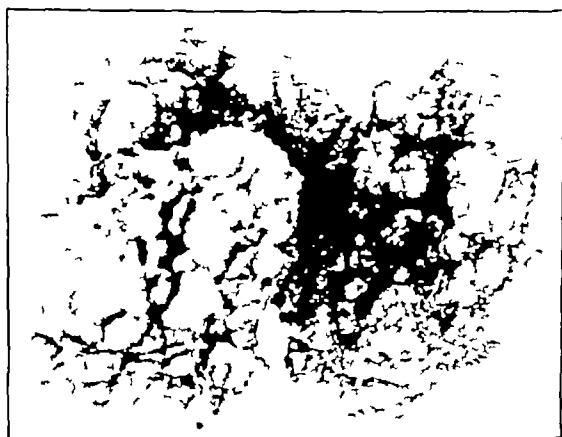


Fig 6—Lobulated villous papilloma of the rectum

occluding the lumen of the bowel (figs 6 and 7). The average size is perhaps 2 to 3 inches (5 to 7.6 cm) above the surface of the bowel. The tumor is very soft, and its color usually resembles that of the normal mucosa surrounding it. When immersed in water the waving, arborescent structure of the tumor is usually apparent. The tumors appear only in adults, as far as I know, and they grow slowly. Rarely they may serve as the apex of an intussusception (fig 8). In 1 of my patients an acute obstruction of the descending colon was produced, but in most patients the tumors make their presence known by hemorrhage, sometimes acute and massive, and by the passage of tremendous amounts of mucus due to the rich development of goblet cells in their structure.

Histologically the structure of the tumor is villous, the elongated branching tubules showing increased cell layers, increased nuclear staining with some mitotic figures and a large increase of the goblet cells of the mucosa (fig 7). Everywhere the relation of the mucosa to the

basement membrane is preserved, and the connective tissue stalk is regular and often runs out into the larger elevations of the tumor. In most of the papillomas adenomatous structures are found at the base

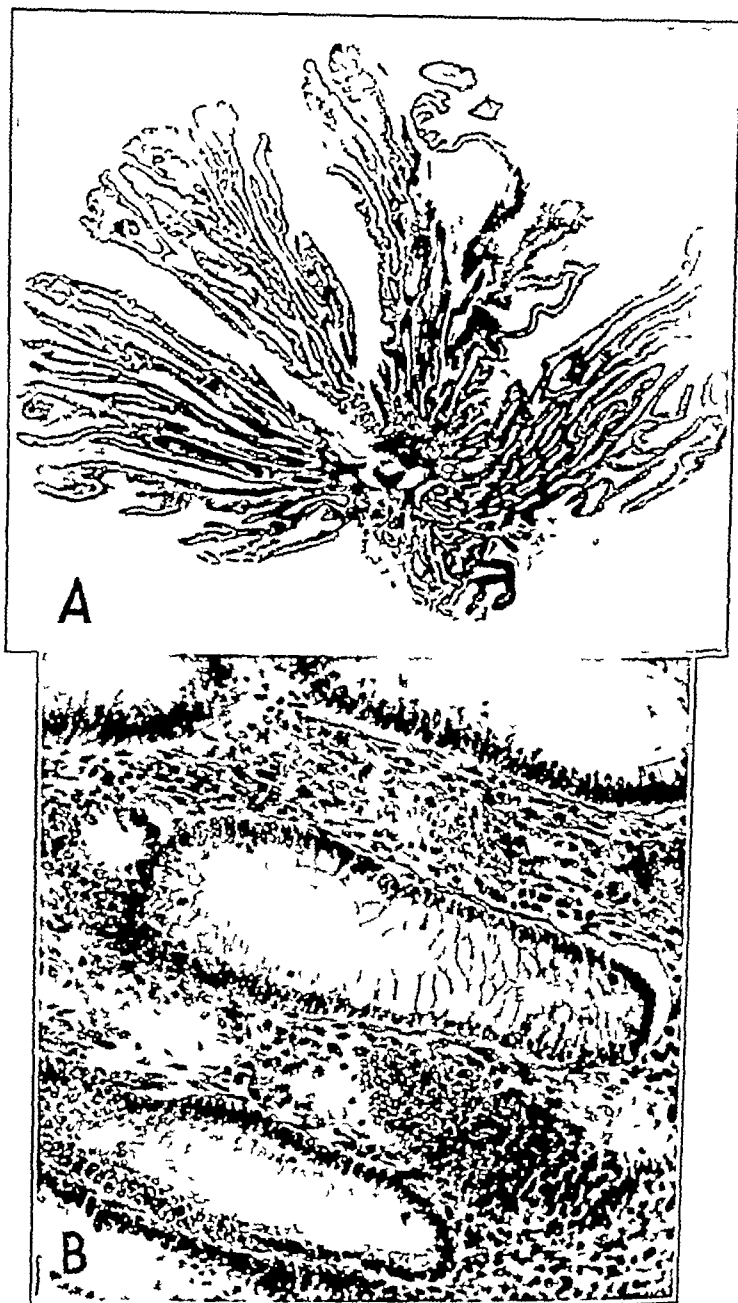


Fig 7—*A*, photomicrograph of the villous structure of tumor shown in figure 6. *B*, high power magnification of the tubules of a villous tumor of the colon, showing increased cell layers, increased goblet cells and mitoses but regular and orderly arrangement of the epithelium in relation to the basement membrane.

of the tumor, some of which are cystic. The tendency to wild, disorganized tissue growth is also found in these tumors, and in 2 of 27 cases I have seen an early carcinoma beginning in the lesion. Many c

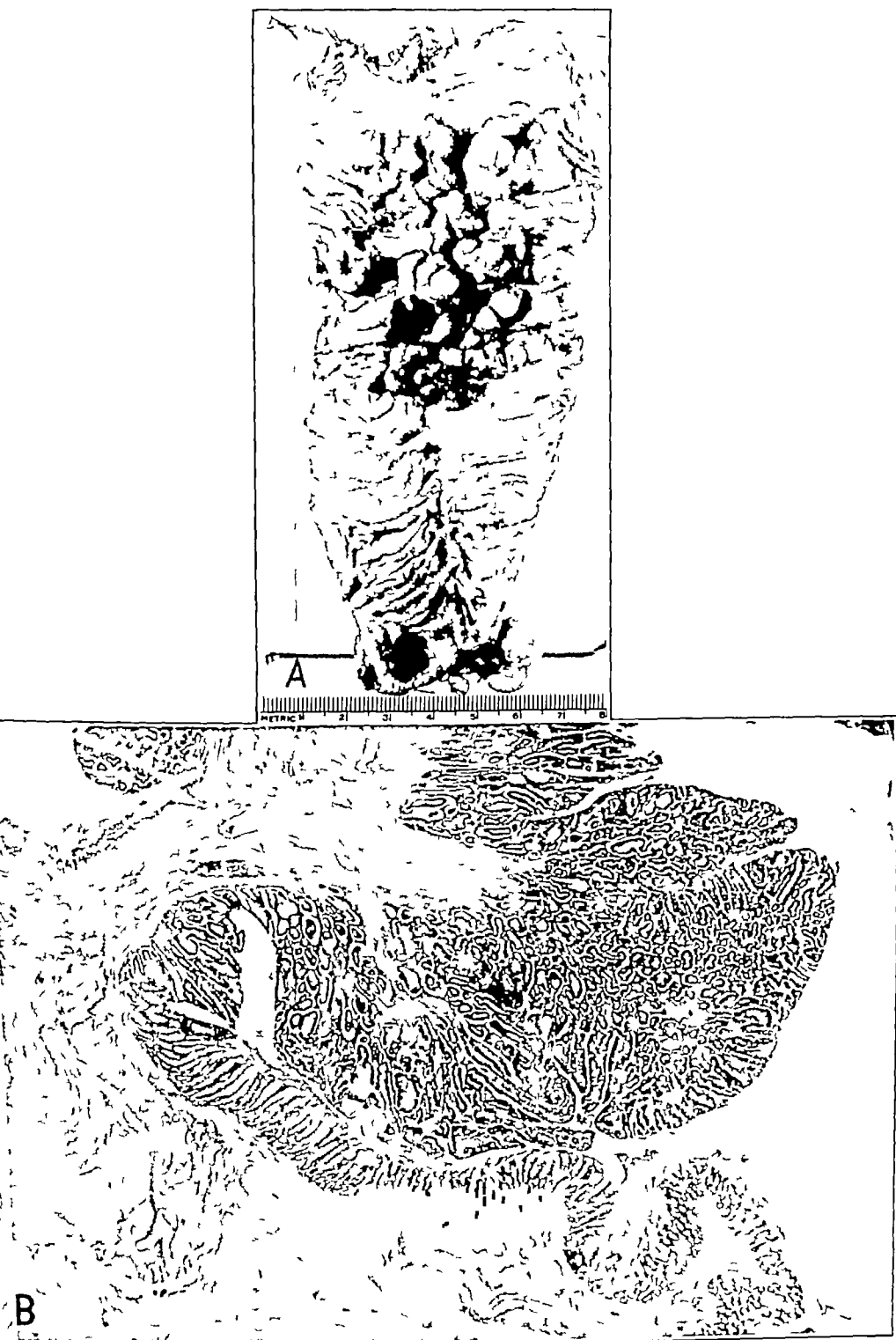


Fig 8—*A*, papilloma of the descending colon producing obstruction *B*, photomicrograph of a portion of the papilloma compared to the normal mucosa of the bowel adjacent to it



these tumors in my early management of them were subjected to repeated fulguration, which is usually inadequate for the larger growths. In none of the repeatedly irritated tumors did malignancy supervene. If removal of these tumors is incomplete, recurrence will promptly supervene, but in my experience the recurrences have been benign histologically. When malignant changes occur in this type of growth they usually occur in the center of the papilloma. Of all the benign polypoid growths occurring in the large bowel, the papilloma most nearly resembles in gross appearance a carcinoma, and, conversely, many carcinomas take on a distinctly papillomatous appearance. In histologic examination of this type of growth it is therefore of particular importance that the whole tumor be examined, as the base and center of the mass are most likely to show carcinomatous changes. Of great importance in determination of the kind of operation (local or radical) to perform are the gross appearance and feel of the tumor, any evidence of induration or ulceration giving clear indication for radical removal of the segment of bowel containing the tumor.

One of the most striking and convincing arguments in favor of the relation of polyps of the large bowel to the development of carcinoma is seen in multiple polyposis. In the presence of this lesion the entire colon and rectum may be studded with polyps, thousands of them, varying in size from a millimeter to several centimeters, with either sessile or pedunculated attachments and with the histologic framework of an adenoma, a papilloma or a mixture of the two (fig 9). In many of the polyps the regular structure in relation to the connective tissue stalk is lost, and the branching tubules with heavily staining multiple-layered cells indicate a tendency to uncontrolled growth. Clinically considered, the only etiologic basis of this bizarre and unusual tendency to tumor formation is a hereditary one, there being a remarkable occurrence of this lesion in successive generations of a family. The other definite and alarming tendency of these polyps is to malignant degeneration, there being not infrequently three to four areas in the colon where carcinoma has developed. In Loring's case (fig 9A) 3 definite carcinomas were found in the colon. This decided tendency to carcinomatous degeneration in multiple polyposis has led nearly all surgeons to advise graded removal of the entire large bowel before carcinoma develops.

Akin to this lesion but lacking the hereditary factor and the extensive involvement of the colon is the occurrence of multiple polyps in the large bowel where 3 to 10 may be present. These are often of varying sizes and may be widely separated. It seems probable that the malignant degeneration of these polyps is responsible for the increasing recognition of multiple cancers of the large bowel. I have observed 5 examples

of double cancer of the large bowel, in 4 of which the condition was highly suggestive of carcinomatous degeneration of polyps. A short history of a case of this kind will be given.

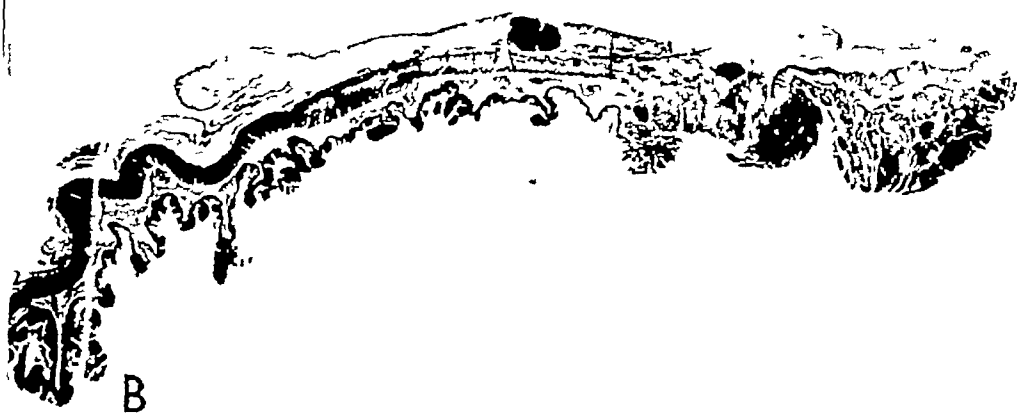


Fig 9—*A*, postmortem specimen of multiple polyposis of the colon which included three separate carcinomas with regional metastases. *B*, giant section of the colon shown in *A* (Dr Mark Loring), showing the various polypoid structures.

A fat man 52 years of age had a definite carcinoma of the ampulla of the rectum in the form of a polypoid mass protruding into the lumen of the bowel which was ulcerated and indurated and from which a biopsy specimen was taken showing definite invasion of cancer cells (fig 10). About 3 inches (7.6 cm) above this lesion was a flat, sessile attached polyp which was not ulcerated and

had every appearance of being benign. No other lesions were suspected, and a fluoroscopic study of the colon revealed no other lesions. A one stage abdomino-perineal resection of the rectum was carried out, with some difficulty due to the adiposity. The patient died of peritonitis. The autopsy revealed 2 other polyps of the transverse colon, one about 2 cm in diameter, with definite carcinomatous degeneration (fig 11).

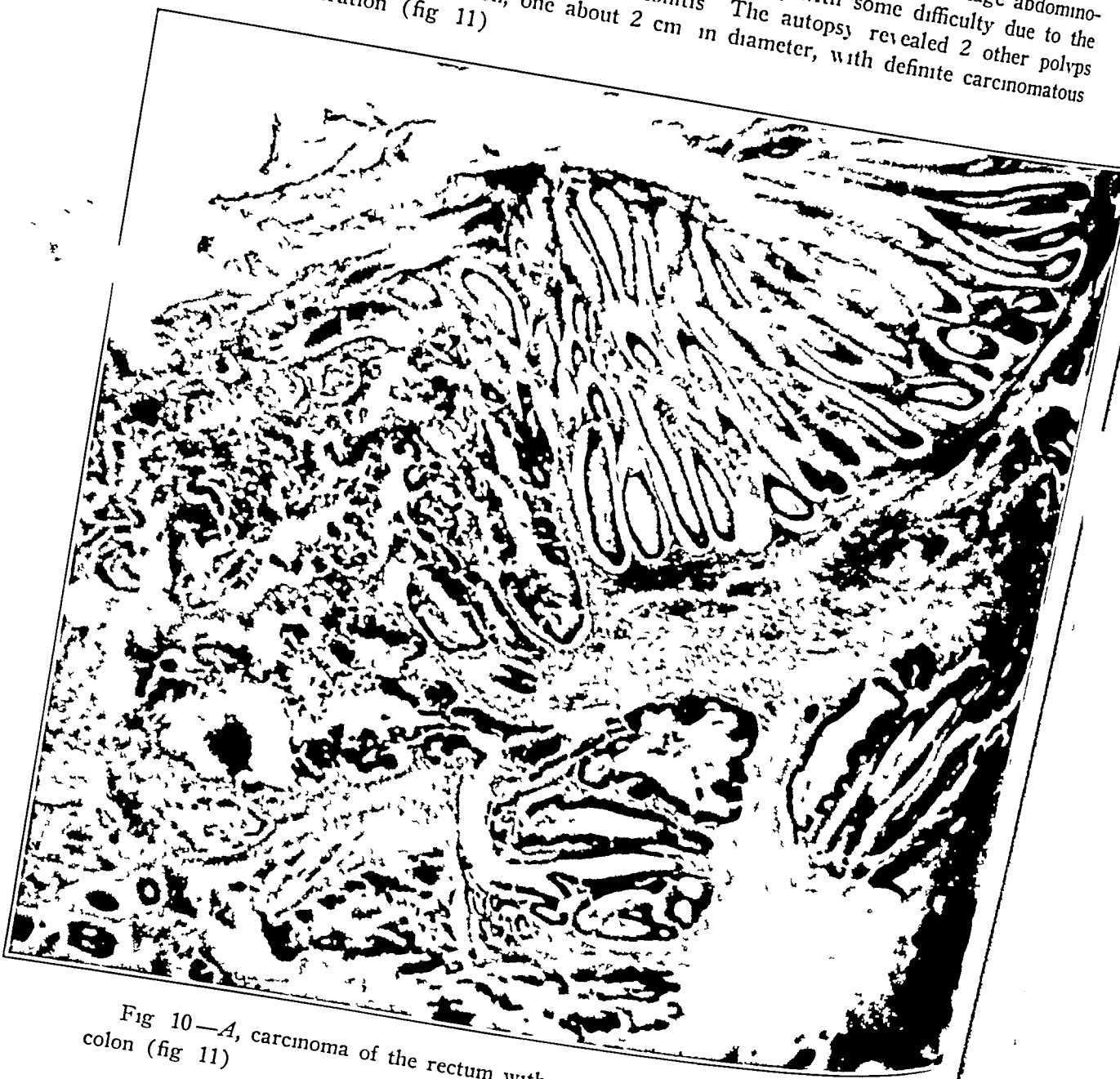


Fig 10—A, carcinoma of the rectum with a malignant polyp of the transverse colon (fig 11)

Dr W B Gabriel, of St Mark's Hospital, London, England, has several interesting specimens illustrating these same points. Of very much less importance or of no importance in their carcinomatous tendency are the so-called lymphoid polyps, which may appear as

multiple slightly elevated flat lesions a few millimeters in diameter, affecting the colon and rectum, and which are really a form of lymphoid hyperplasia (fig 12 *A*)

Of more clinical interest but lacking carcinomatous tendencies are the large lymph polyps, of which I have seen 5 instances in the rectum

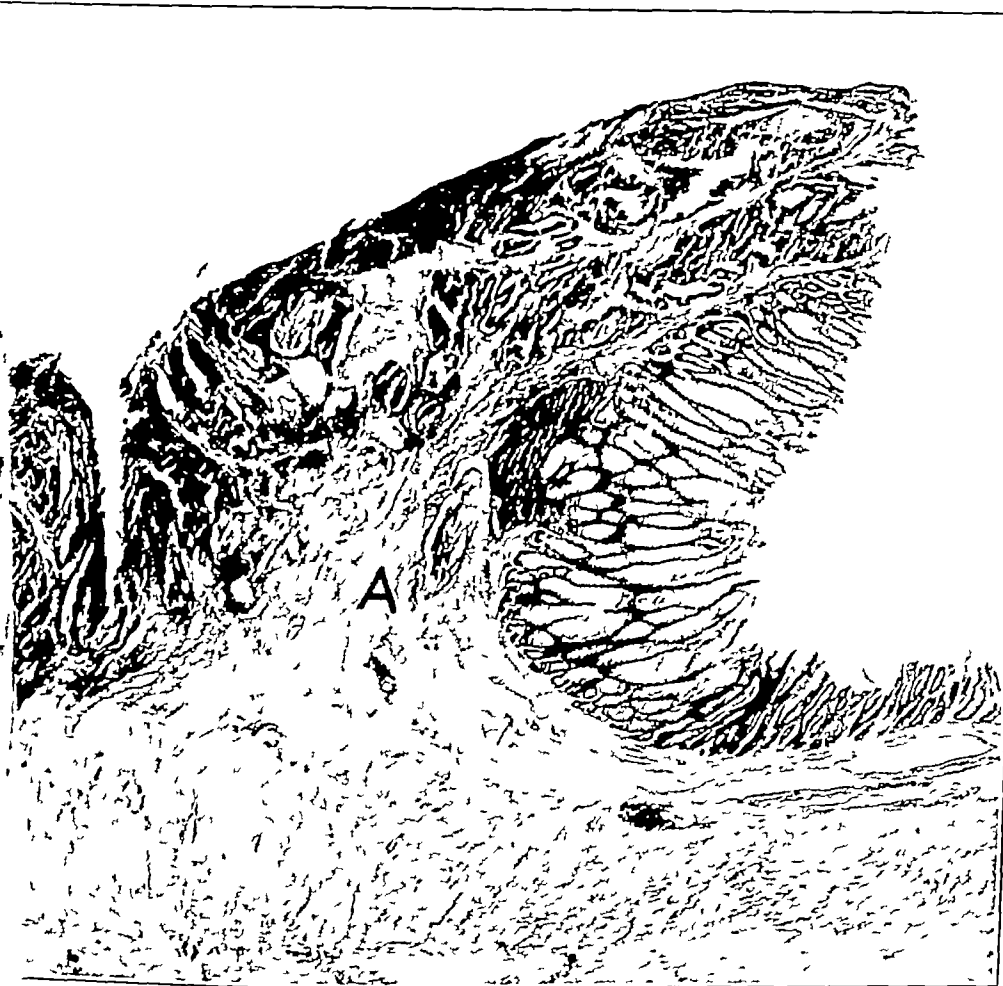


Fig 11—Malignant polyp of the transverse colon associated with carcinoma of the rectum. Note the invasion of the tumor through the muscularis mucosa at *A*.

In the first 2 cases there was a single polyp in the rectum, about 2 cm in diameter, with sessile attachment. The tumor was rather hard. In appearance the mucosa over the polyp was normal, and it appeared as if a globular mass were situated in the bowel, immediately beneath the

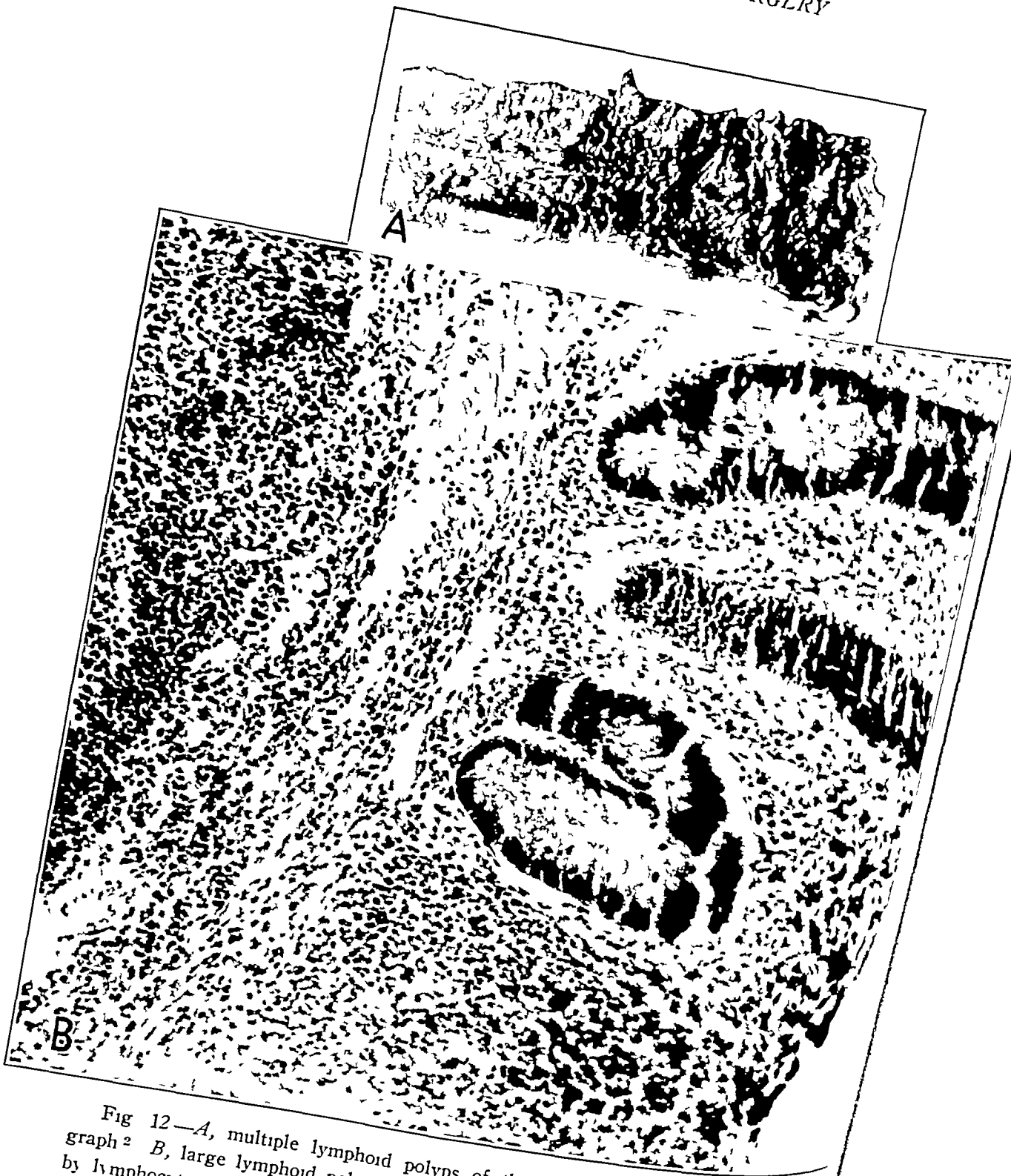


Fig 12—*A*, multiple lymphoid polyps of the colon, from Westhues' monograph; *B*, large lymphoid polyp of the rectum with epithelial tubules separated by lymphocytic infiltration.

mucosa On removal of the mass the feeling was substantiated, on microscopic examination the mucosa was normal, but beneath it was a large accumulation of lymphoid tissue (fig 12 B) This may have been a simple inflammatory hyperplasia of the normal lymphoid tissue

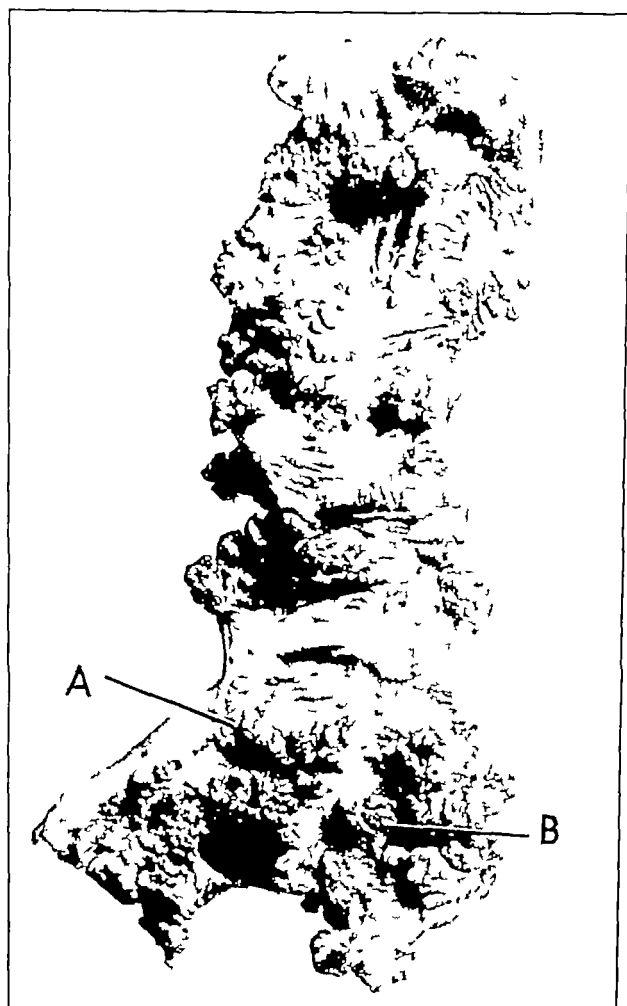


Fig 13—Multiple inflammatory polyps of various types found in a colon which was the seat of amebic ulceration

A third case was more confusing A woman 50 years of age was referred to me with the probable diagnosis of carcinoma of the rectum On examination a mass about 4 cm in diameter, consisting of 2 definite polypoid masses, was present on the anterior wall of the rectum about 3 inches (7.6 cm) from the anus The patient had been bleeding and

through the proctoscope it was seen that the base of the polypoid mass was ulcerated, though the major portion of the mass was covered with smooth epithelium. A biopsy specimen taken through the ulcerated area revealed evidence of a lymphoid polyp covered with epithelium, without adenomatous or papillomatous degeneration. Complete removal of the mass showed a typical lymphoid polyp. Whether the ulceration of the lesion had any potentialities as far as carcinoma is concerned is hard to say.

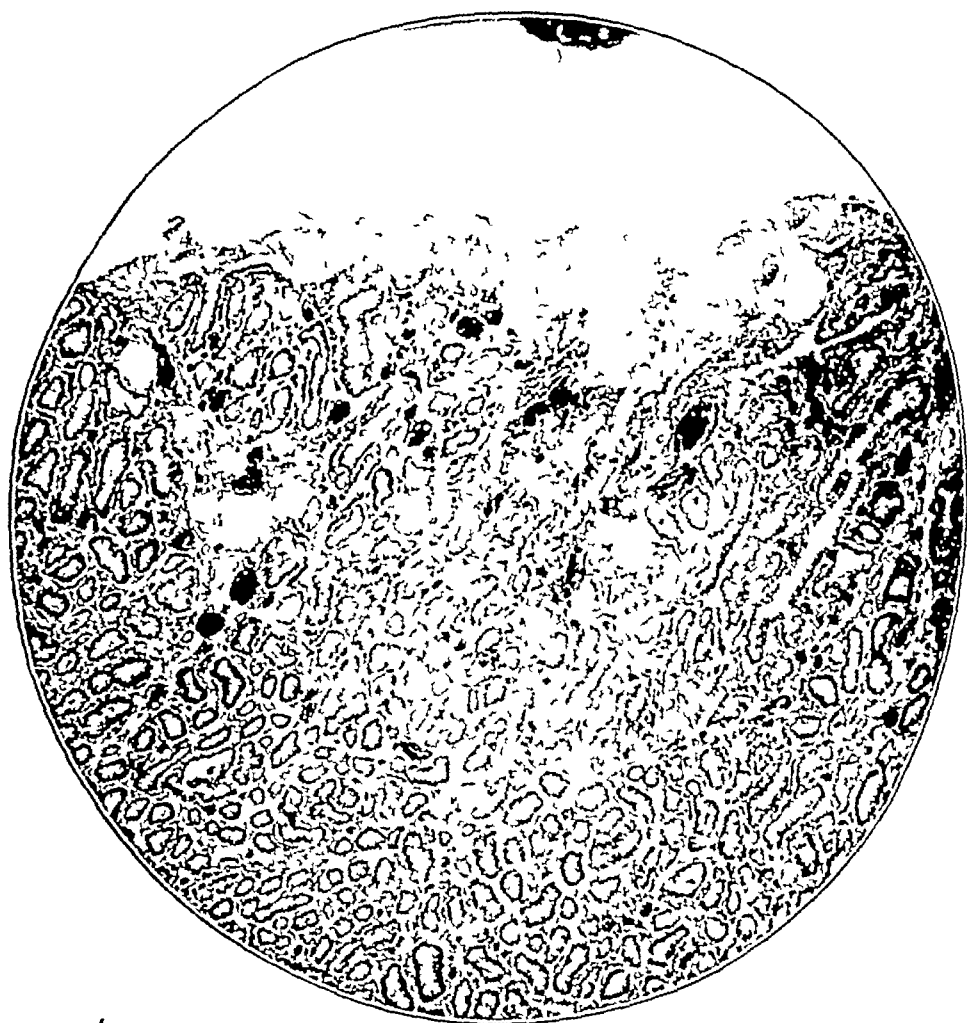


Fig. 14—Section through *A* in figure 13, which shows hyperplasia of the epithelial elements of the mucosa as well as an inflammatory process in the otherwise normal mucosa.

The last classification of polyps involving the large bowel is the inflammatory type, to which some reference has been made. The most striking examples of inflammatory polyps are those seen following extensive destruction of the mucosa of the bowel as a result of amebic dysentery or ulcerative colitis (figs 13, 14 and 15). The polyps result from an inflammatory hyperplasia of persistent small islands of mucosa between

areas of ulceration One patient had such a polyp as large as a goose egg in the rectum, which he would not allow to be removed

One of the most interesting examples of this type of polyp was seen in a man 38 years of age The level of hemoglobin had dropped to 28 per cent owing to repeated bleeding from the rectum By proctoscopic examination, at 12 cm from the anus an inflamed area with numerous finely lobulated papillomatous tumors was seen Unfortunately no biopsy was done A colostomy was performed, and on repeated proctoscopic examination a gradual recession of the papillary tumors



Fig 15—Section through *B* in figure 13, showing a polypoid tumor with a connective tissue stalk and branching epithelial tubules with heavily staining nuclei This polyp developed in the presence and probably as the result of chronic inflammation of the intestinal mucosa from amebic dysentery Its appearance cannot be distinguished from that of the adenomatous polyps which are called true tumors

took place until, at the end of ten months, no tumor was visible, and the bowel appeared practically normal About nine months after colostomy several elevated polypoid masses, each about 0.5 cm in diameter, appeared on the exposed mucosa of the colostomy stoma One was excised, and a section was made This cor-



responded to the inflammatory hyperplasia already described. At the request of the patient the colostomy stoma was closed. Bleeding again appeared, and the rectum showed marked inflammation without tumor formation. The rectum was removed. No evidence of tumor growth was found. This patient well exemplifies the influence of inflammation on hyperplasia of the mucosa of the colon, which closely resembles tumor formation.

One of the most interesting examples of the influence of inflammation on changes in the epithelium of the large bowel was readily seen at postmortem examination of a woman who had suffered with amebic dysentery for three years. The bowel showed many discrete ulcers from which amebas were isolated. The sigmoid flexure of the colon and the rectum particularly were the sites of numerous polypoid changes, ranging from small millimeter elevations to well developed flat and pedunculated tumors. Histologic examination of the bowel showed widespread inflammation of the mucosa with desquamation or necrosis of the surface cells. The elevations and tumor-like growths on the mucosa ranged from simple hyperplasia in which reduplications of the elements of the mucosa without increased staining of the cells were seen to typical adenoma formation with a connective tissue stalk and branching tubules with heavily staining nuclei. The sections referred to are shown in figures 14 and 15. In this case the whole problem of the relation of inflammation to tumor formation is brought acutely into focus.

One other example of this relation must be mentioned. A young woman in her late twenties had suffered from extensive ulcerative colitis for several years. Proctoscopic examination by her physician in Ann Arbor, Mich., because of first bleeding revealed a small papillary tumor at the rectosigmoid juncture. This was completely removed through the proctoscope and after examination by the late Dr. A. Warthin was pronounced carcinoma. Shortly afterward I examined the patient proctoscopically but could find no lesion except extensive ulcerative colitis. Within two months another examination revealed a small carcinoma at the rectosigmoid juncture. It is, of course, impossible to prove that the original tumor was an inflammatory polyp which had undergone malignant degeneration, but the whole course of events is of more than ordinary interest.

The various types of polypoid growths occurring in the large bowel having been reviewed and their inclination to carcinoma formation having been indicated in a general way, the results of Fevrter's study of 1100 colons containing 1,017 polyps may be interesting. He found no case of multiple polyposis and none of papilloma. There were 15 patients in whom carcinoma of the colon was the cause of death and 4 in whom latent carcinoma was present. In 350 patients with

polyps of the colon, 6 of the polyps were carcinomatous histologically and 4 were suggestive of carcinoma. Of 1,017 polyps of the colon from 1,800 autopsies

	Per Cent
762 were millet seed size	75
175 were pea size	17
35 were cherry stone size	3.5
22 were hazelnut size	2.2
5 were cherry size	0.5
4 were almond size	0.4
8 were bean size	0.8
7 were larger	0.7

If adenomas alone are considered

Age, Years	Males	Females
0 to 14 in 100 cases	No polyps	No polyps
15 to 34 in 100 cases	No polyps	1 polyp
35 to 44 in 100 cases	2 polyps	4 polyps
45 to 54 in $\frac{1}{8}$ of the cases	polyps	$\frac{1}{10}$ had polyps
55 to 64 in $\frac{1}{4}$ of the cases	polyps	$\frac{1}{10}$ had polyps
65 to 74 in $\frac{1}{3}$ of the cases	polyps	$\frac{1}{8}$ had polyps
75 to 87 in $\frac{1}{3}$ of the cases	polyps	$\frac{1}{3}$ had polyps

If age (in years) is considered for all of the lesions found

Age, Years

0 to 14	Of 100 patients, 2 had polyps
15 to 34	Of 100 patients, 5 had polyps
35 to 44	$\frac{1}{6}$ of the patients had polyps
45 to 54	$\frac{1}{3}$ of the patients had polyps
55 to 64	$\frac{1}{2}$ of the patients had polyps
65 to 74	$\frac{2}{3}$ of the patients had polyps
75 to 87	$\frac{3}{4}$ of the patients had polyps

As a result of this thoroughgoing study, Feyrter has called attention to the polypoid lesions in which little histologic evidence of change from normal epithelium is present and also to polyps in which more or less lack of differentiation of epithelium, lack of order of the epithelial elements, differences in the depth of cell layers and marked differences of staining qualities of the cells and nuclei exist. He has stated that one must differentiate between hyperplasia that remains such, hyperplasia that develops into an adenoma and hyperplasia that develops into a cancer. He holds with Oberdorfer and Lubarsch that infiltrating destructive growth is the principal sign of cancer. The other signs of increased activity of epithelial growth are suggestive but offer no proof.

Westhues<sup>2</sup> has studied 100 cases of rectal carcinoma with accompanying polyps and an unstated number of polyps of the rectum and

mucosa. These changes are mostly seen on the periphery of the adenoma. In no area could invasion be said to have taken place, but if certain fields in these polyps are compared to fields in a proved carcinoma it would be difficult to distinguish between them (fig 16). This emphasizes anew the importance of having the whole tumor to examine and of ascertaining the appearance and consistency of the polyps so that areas of ulceration or induration can be determined.



Fig 16—Bizarre epithelial arrangement with little differentiation, resembling carcinoma, in a polyp of the rectum which was neither indurated nor ulcerated. Local removal of the polyp resulted in cure.

There were 3 small adenomas (1 to 2 cm in diameter) under going early malignant changes. This was suspected by slight ulceration of the lesion. In 2 of these the carcinomatous ulcer was not more than 2 mm in diameter, and in the third the pedunculated adenoma was superficially ulcerated (figs 17, 18 and 19). These constitute the earliest evidence of malignancy in the rectum which I have seen.

There were 4 large flat adenomas 8 to 6 cm in diameter, in which malignancy was suspected but very difficult to prove until after radical

In the group of 27 flat-based papillomas or villous tumors occurring for the most part in the rectum, their histologic character and structure is in general more complicated than in adenomas of the bowel. The long, many-branching tubules, with many-layered cells, increased staining properties and nuclear mitoses, indicate active growth. Grossly



Fig 18—Junction of the adenoma and the carcinomatous ulcer shown in figure 17

these tumors become large, some being as large as the adult fist and obstructing the bowel. They may remain in the bowel for years without undergoing malignant change, although grossly they have a striking resemblance to carcinoma. When malignant changes occur in the

tumors, the depth and not the periphery of the tumor is apt to be involved, and an area of induration develops (fig 23). Biopsy of a specimen of the papilloma surrounding this area may show perfectly benign noninvasive papilloma, but biopsy of a specimen taken through the area of induration reveals infiltrating carcinoma. Papillomas, because



Fig 19—Two millimeter carcinomatous ulcer on a pedunculated adenoma

of the evidence of epithelial growth changes, as deeply staining many-layered cells, mitoses and branching tubules, are often called carcinoma grade I. This, to my mind, is an error, for ulceration and invasion are the only certain criteria of malignancy. It should in fairness be stated that in about half of my specimens some loss of differentiation of the tubular epithelium was present and that there was less regular

relation of the epithelium to the connective tissue stalk and the muscularis mucosa than is normal. In view of the fact that these tumors are undoubtedly premalignant, they must be thoroughly removed, but local removal is indicated whenever possible if no induration or ulceration



Fig. 20—Soft, large, flat tumor of the rectum. This type of growth is hard to diagnose as to malignancy or benignity.

tion of the tumor is present. It is pertinent to say that among these 27 cases no malignancy has occurred after local removal of the tumor. In 3 cases local recurrence of the papilloma took place, but after removal of the recurrent growth the patients have been well for periods varying from two to six years.

In my table, group V is listed as polyps with early malignancy. Three of these were concerned with papillomatous soft growths in the rectum, where slight induration was present. Biopsy of material from these areas showed invading carcinoma, and radical operations were carried out.

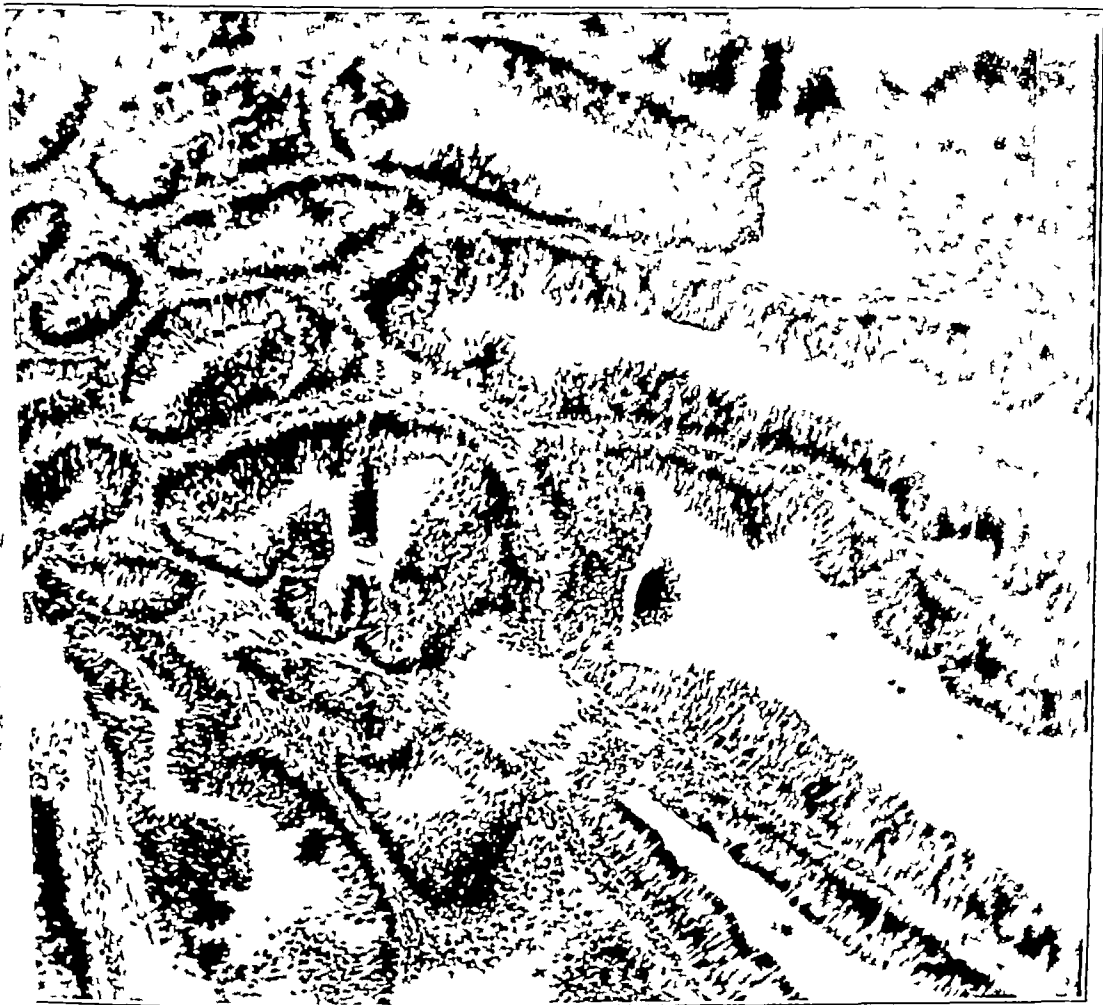


Fig 21—Biopsy of the surface of the tumor in figure 20 was suggestive of carcinoma, but the diagnosis was not certain.

#### SUMMARY AND CONCLUSIONS

It can be fairly said that in the mucosa of the large bowel there is a gross and gradual histologic transition from hyperplasia to adenoma or papilloma to carcinoma. Whether the inherent tendency to carcinoma in any one of these lesions is present from the start is not known.

Carcinomatous changes in these lesions can be safely diagnosed only by gross evidence of induration or ulceration and by histologic evidence of invasion, in which instance tumor cells are found breaking through the muscularis mucosa



Fig 22—After radical removal of the tumor in figure 20, sections taken through the base of the tumor showed typical carcinomatous infiltration

While many of the polyps of the colon remain benign for years, they cannot be trusted to do so and should be thoroughly removed, locally if benign and radically if evidence of malignancy exists



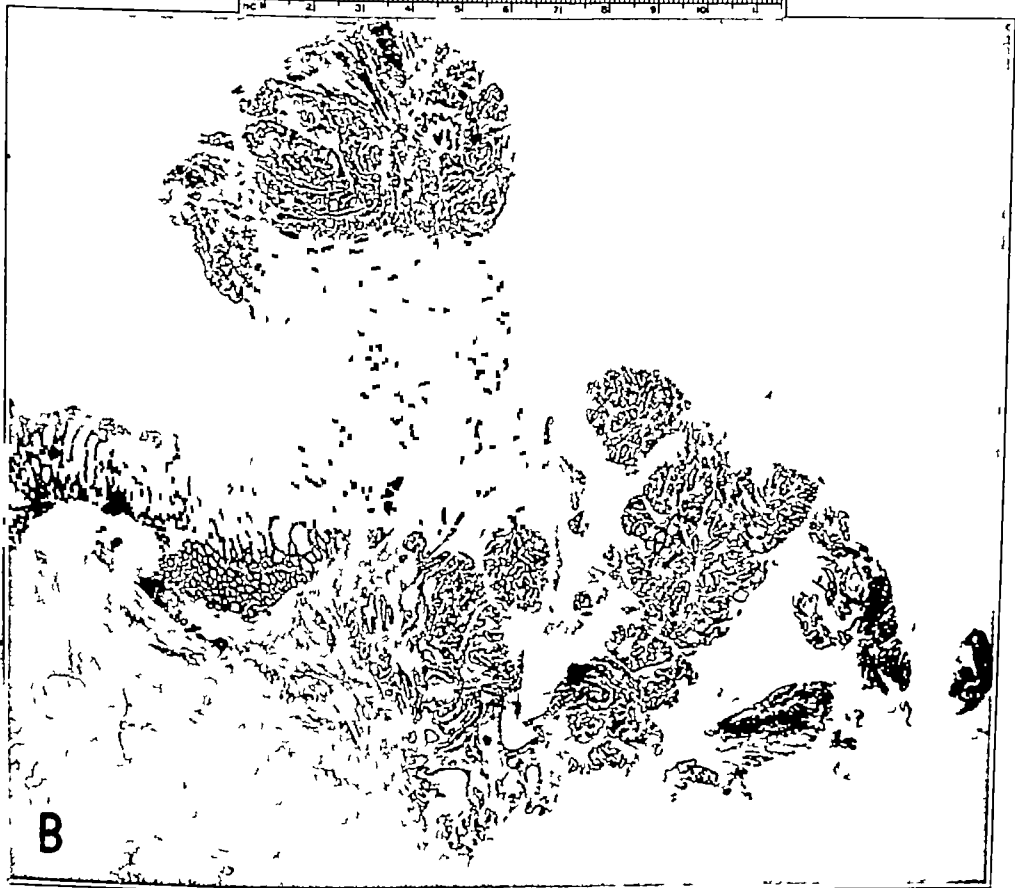


Fig 23—*A*, diffuse adenomatous tumor of the rectosigmoid juncture in a 23 year old woman. Its malignancy was questionable *B*, photomicrograph of the tumor, showing definite carcinomatous infiltration

The results of biopsy may not be conclusive for diagnosis unless the material is taken from an area of ulceration or induration. It is impossible with many of these lesions for a pathologist to make a diagnosis of malignancy or benignity from a small piece of tissue taken at random. It is better to examine the whole tumor.

The earliest carcinomas I have seen in the large bowel are 1 to 2 mm ulcerating lesions found on polyps.

# BARBERRY

ANCIENT REMEDY, NEW GERMICIDE

GEORGE F DICK, M D

CHICAGO

Some time ago Mr William H Wood, of Brownsville, Texas, called my attention to infusion of algerita root, a remedy used by the Indians of Texas and Mexico for many ailments

As many of these ailments were infectious processes, the following experiment was carried out in order to learn whether the infusion possessed any antiseptic or germicidal properties

## METHOD

Five hundred grams of crushed algerita root was boiled for thirty minutes in 2 liters of distilled water and the liquid filtered through gauze This infusion was sterilized in the autoclave and used as follows One-tenth cubic centimeter of a twenty-four hour broth culture of scarlet fever streptococcus was added to each of six test tubes, each containing 10 cc of ordinary nutrient broth with 0.1 cc of sterile blood added To one of these tubes 0.1 cc of algerita root infusion was added, to four tubes, 0.2 cc, 0.5 cc, 1.0 cc. and 3.0 cc, respectively, was added, and to the remaining tube no infusion was added The six tubes were incubated for twenty-four hours, then 0.1 cc of the well mixed contents of each tube was added to 10 cc of broth, and 0.1 cc of this broth was added to 10 cc. of melted nutrient agar at 40 C with 0.5 cc of blood added Blood agar plates were poured and incubated for twenty-four hours

The Petri plate of the control tube, with no infusion added, contained innumerable colonies of streptococci at the end of the incubation period The Petri plate of the culture tube containing 0.1 cc of infusion showed a few colonies of streptococci, and the remaining plates contained no growth

It will be noted that in plating out the mixture of infusion being tested, bacterial suspension and broth, a dilution of 1:100 was made, which did away with any inhibitory action of small amounts of infusion carried over into the agar plates

The experiment indicated, therefore, that the algerita root infusion was germicidal in the tubes containing 0.2 cc or more Repetition of this experiment gave consistent results

In order to find out the length of time required to kill streptococci, 0.5 cc of a twenty-four hour broth culture of erysipelas streptococcus was added to 10 cc of nutrient broth containing 0.5 cc of algerita infusion The mixture was incubated after thirty minutes 0.1 cc of the mixture was added to 10 cc of broth, and

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From the Department of Medicine, University of Chicago

0.1 cc of this mixture was plated out. In a similar way, 0.1 cc of the mixture was plated out after one, two, four, seven, sixteen and twenty-four hours. All the plates up to those made after seven hours contained many colonies, when only 115 colonies were found, in sixteen hours 10 colonies were found, and in twenty-four hours no growth was present.

In the dilution used, (1:20), then, the streptococci were killed only after seven to twenty-four hours of contact.

With various dilutions of mercury bichloride used in the same way as the infusion was used in the second experiment, 0.5 cc of a 1:10,000 solution of mercury bichloride added to 0.1 cc of twenty-four hour culture of erysipelas streptococcus in 10 cc of broth took eight hours to kill, so that the infusion has about the same germicidal power as a 1:10,000 solution of mercury bichloride.

Experiments were carried out to compare the action of alginate infusion on different bacteria. These tests were done just as was done with scarlet fever streptococci except for the variety of organisms used. The result is shown in the accompanying table.

*Effect of Infusion on Different Bacteria*

Organism	Broth and Bacteria Alone	Number of Colonies Growing on Plates After 24 to 48 Hours with Different Quantities of Infusion					
		0.1 Cc	0.2 Cc	0.5 Cc	1 Cc.	2 Cc	3 Cc
Hemolytic streptococcus of tonsillitis	Innumerable	Many	0	0	0	0	0
Scarlet fever streptococcus	Innumerable	10	0	0	0	0	0
Pneumococcus type I	Innumerable	Many	Many	70	0	0	0
Staphylococcus	Innumerable	Innumerable	Innumerable	150	15	0	0
Streptococcus viridans	Innumerable	Many	Many	Many	0	0	0
Typhoid bacillus	Innumerable	All plates contained as many colonies as control					
Diphtheria bacillus	Innumerable	0	0	0	0	0	0
Brucella melitensis	Innumerable	Many	Many	Many	3	0	0
Erysipelas streptococcus	Innumerable	Many	50	0	0	0	0
Brucella abortus	Innumerable	Many	Many	6	0	0	0

It will be noted at once that there is a very interesting selective action, for in the tubes containing 0.2 cc of infusion, hemolytic streptococci and diphtheria bacilli were killed, whereas staphylococci and pneumococci required about five times as much infusion. The brucella organisms were between the other two groups, while typhoid bacilli grew as well in all concentrations used as in nutrient broth alone. It was also observed that the infusion had to be kept under sterile precautions or preservatives added to prevent the growth of molds.

In view of the remarkable selective germicidal action of the infusion, it seemed worth while to investigate its toxicity for animals.

A rabbit weighing 2,075 Gm was given 0.3 cc of filtered sterile infusion intravenously on April 4, 1939. Three days later the same animal was given 4 cc. Some convulsive movements were noted, but the animal remained well.

December 26 (about seven months later), when it weighed 2,879 Gm and had normal urine. Between Jan 1 and March 4, 1940, 1 cc was given intravenously three or four days a week, in all, 21 cc. On April 25 the rabbit seemed well, weighed 2,841 Gm and had normal urine.

Two rabbits were given 20 cc of infusion by stomach tube daily for two weeks and remained apparently well until observation ceased, four months later. On the other hand, 2 rabbits receiving 5 cc intravenously died at once.

Amounts up to 0.2 cc may be given to mice subcutaneously without effect, but 0.3 cc. occasionally proves fatal, and 0.5 cc or more kills regularly.

#### COMMENT

These experiments, together with reports that the Indians and old settlers in Texas take by mouth amounts of the infusion up to several ounces three times a day, show that algerita root infusion has considerable germicidal power, with a relatively low toxicity.

On looking up the botanic classification of the algerita bush, it was found to belong to the large barberry family of shrubs, which has an extremely wide distribution in the world. *Algerita* is also known as *Berberis trifoliatis*, *Mahonia trifoliata* and *Odosteman trifoliatis*.

Hart<sup>1</sup> stated that algerita root has long been used by old settlers and Indians in Mexico and Texas for sore eyes, sore mouth, cutaneous diseases and gonorrhea. He analyzed the root and found that it contained 1.49 per cent of berberine ( $C_{20}H_{19}NO_3$ ), a yellow dye characteristic of the barberry family. Unlike *Berberis vulgaris*, however, it contained no hydrastine.

Chopra<sup>2</sup> listed several varieties of barberry, including *Berberis lycium* and *Berberis aristata*, used in India by the natives for various ailments, including malaria, syphilis, oriental boil and duodenal ulcer.

According to Culbreth,<sup>3</sup> *Berberis canadensis* was official from 1860 to 1880 and was used for dysentery, dropsy and many other diseases. Other plants containing berberine, such as calumba and goldenseal, are used in Africa, Madagascar and other parts of the world for malaria and various fevers.

Cushny<sup>4</sup> stated that the main pharmacologic action of the drugs containing berberine is that of a bitter tonic and that berberine, aside from its bitter taste, has no pharmacologic action.

1 Hart, M. C. *Am J Pharm* 88 301, 1916.

2 Chopra, R. N. *Indigenous Plants of India: Their Medical and Economic Aspects*, Calcutta, Art Press, 1933.

3 Culbreth, D. M. R. *A Manual of Materia Medica and Pharmacology*, ed 4, Philadelphia, Lea Brothers & Co., 1906.

4 Cushny, A. R. *Textbook of Pharmacology and Therapeutics*, ed 9, Philadelphia, Lea & Febiger, 1928.

Flückiger and Hanbury<sup>5</sup> stated that *Berberis lycium* was used by the ancient Greek and Roman physicians, and it is mentioned by Dioscorides, Pliny and Celsus. It was particularly valued for sore eyes and catarrhal diseases.

The only instance of an adequate investigation of germicidal properties of berberis on its products is to be found in a report by Das Gupta<sup>6</sup> and another by Warma<sup>7</sup> on the use of 3 cc of a 2 per cent solution of berberine acid sulfate injected into the lesions of oriental boil. According to Das Gupta, the injections are followed by rapid disappearance in biopsy specimens of the Leishman-Donovan bodies and rapid clinical improvement. Others have confirmed these observations. That the germicidal properties of algerita root infusion are probably due to its berberine content is shown by substituting a 0.1 per cent solution of berberine sulfate Merck for the algerita infusion as described. It was found that from 0.05 cc to 0.1 cc of the 1 per cent berberine solution in 10 cc of broth with 0.1 cc of *Erysipelas streptococcus* twenty-four hour broth culture regularly killed the bacteria, whereas it took about 0.2 cc of the infusion to kill the same organism. The berberine content of the infusion is about  $\frac{1}{4}$  of 1 per cent, so that it is unnecessary to assume any other germicidal substance in the infusion other than berberine.

It was also found that the time required for a 1 per cent solution of berberine to kill *Erysipelas streptococci* was about eight hours in the dilution described, and this is from one-half to one-fourth the time required for the infusion to produce the same result.

Chopra<sup>2</sup> gave 0.1 Gm per kilogram of body weight as a fatal dose for rabbits. I found that 0.01 to 0.02 Gm per kilogram was sometimes fatal if given intravenously, and 0.0005 to 0.0010 Gm was fatal for mice. On the other hand, a rabbit weighing 2.415 Gm received 0.01 Gm intravenously daily for twenty days with no evidence of harm. Merck's index gives the dose of berberine sulfate as 0.5 to 1.0 Gm three times a day.

It is apparent, then, that berberine, while relatively nontoxic by mouth, is, like the crude infusion of algerita root, unsafe for intravenous use except in small doses.

It is interesting that the barberry family of shrubs has been used by aborigines in many parts of the world for many ailments and dis-

5 Flückiger, F. A., and Hanbury, D. *Pharmacographia*. A History of the Principal Drugs of Vegetable Origin Met with in Great Britain and British India, vol. 2, London, Macmillan & Co., 1879.

6 Das Gupta, B. M. *Indian M. Gaz.* 65: 683, 1930.

7 Warma, J. D. *Indian M. Gaz.* 66: 386, 1931.

use has been carried over into the medical profession from time to time as far back as medical history goes, but no report of an adequate investigation of the germicidal action of the substance is to be found

As both crude infusion of *Berberis trifoliatis* and berberine are of low toxicity except on intravenous injection, they would seem to offer some promise, particularly for surface infections. I have used the infusion for such infections as are associated with decubitus and varicose ulcers, tonsillitis and stomatitis, and, while results are promising, more experience is required to warrant conclusions as to its value

# SURGERY OF THE GALLBLADDER IN 1910 AND TODAY

EARLE DRENNEN, M D  
BIRMINGHAM, ALA

A survey of the progress and changes in the management of disease of the biliary tract during the past thirty years presents an interesting panorama

In general, progress in medicine and surgery has been dependent to a large degree on new discoveries and improvements in the ancillary sciences. In the lifetime of the present generation probably most progress has been due to good research work by physicians themselves. The great question which agitated the surgical world from 1900 to 1910 was that of cholecystectomy versus cholecystostomy. Today it is no longer even discussed, cholecystostomy has become a rare and almost discarded operation and when employed is considered a makeshift procedure.

Certainly, the most dramatic and useful development in the diagnosis of disease of the gallbladder during this period was the introduction by Graham and his associates of cholecystography. This was first presented in 1924 and was perfected in 1925. It has since become a standard requirement in the diagnosis of biliary tissue.

It may be worth while, in order to appreciate the distance surgeons have come, to take stock of the equipment which the surgeon of 1910 had for the diagnosis and treatment of diseases of the biliary tract.

In the matter of diagnosis, the patient's history then, as today, was of paramount importance. In fact, a good history properly taken can accurately make the correct diagnosis.

A history of biliary colic, particularly if repeated, with residual soreness over the region of the gallbladder still points definitely to disease of the gallbladder. Also, slight and transient jaundice following such an attack is most suggestive. However, in the earlier period the milder degrees of cholecystitis were overlooked or were attributed to other, nonsurgical conditions. It is in detecting these early conditions and treating them that great progress has been made. If medical treatment fails to bring relief, surgical intervention can now be used safely.

The surgeon of 1910 had only poor roentgenograms, which were seldom conclusive. To his credit, he depended more on the five senses in all diagnostic work than do surgeons of today. For him there was no duodenal tube to pick up crystals of bile salts and pus from the



papilla of Vater to make the diagnosis of stone in the common duct. The van den Bergh test to help locate the origin of jaundice had not yet come to light.

Aschoff's ideas of the origin of gallstones and of the physiology of the liver have been promulgated and generally accepted. In his work on pathology he stated that there are two kinds of gallstones:

the pure cholesterol gall stone, which may occur without symptoms in a gall bladder with normal walls, and may exist in this state for a long period of time, and, as a result of the migration of organisms, or obstruction to the outlet, infection may be superimposed and inflammatory gall bladder disease result.

Under the influence of inflammatory exudate of the mucous membrane, which is rich in calcium, and of the infectious decomposition of the bile, there occurs precipitation of pigment, calcium masses around the cholesterol stone, and thus originates the so-called combination stone from a nucleus of pure cholesterol, not of inflammatory origin.

Also, from his conception of bile formation has come the van den Bergh test, which indicates whether the jaundice is due to obstruction or whether it is of hematogenous origin. In most instances it is of no practical help to the surgeon.

Painless jaundice of increasing severity is nearly always due to cancer of the head of the pancreas or in the bile ducts. The work of Allen Whipple in resecting the head of the pancreas for relief of the condition is a noteworthy and recent achievement in this field.

It has long been known that the jaundiced patient is prone to bleed excessively. The surgeon of 1910 did not have the valuable weapon of transfusion to combat the menaces of hemorrhage and shock. Crile was leading the fight in giving transfusions by joining the artery of the donor to the vein of the recipient. The idea was good, but the procedure was technically futile. Jaundice was formerly believed to result almost wholly from obstructive causes resulting in back pressure on the liver. It was also believed that bile was made only by the polygonal cells of the liver.

Following the work of Aschoff and his conception of the reticulo-endothelial system, a different idea of jaundice has come about. He has stated that the Kupffer cells, which line the venous sinuses of the liver, are phagocytic, taking up hemoglobin and other detritus and turning them into bilirubin. He has also expressed the belief that the parenchymal cells merely secrete the bile and do not form it as was formerly thought. The experiments of Mann completely confirm Aschoff's theory in this matter. Today, with perfected transfusion of blood and with vitamin K, one has much better control over the bleeding and oozing of jaundiced tissues.

It is believed today that the bleeding tendency in jaundiced patients is largely due to deficiency of prothrombin in the blood. Walton stated

that the bleeding tendency from jaundice is a myth. Since vitamin K is fat soluble, it cannot be absorbed in cases of obstructive jaundice for lack of bile in the intestines. Vitamin K normally occurs in green, leafy plants, such as spinach and alfalfa.

As to blood clotting, it is believed that thromboplastin and the calcium ion unite to convert prothrombin into thrombin and also that certain amounts of thrombin will change proportional amounts of fibrogen into fibrin, thus establishing the structural basis of the clot. Since vitamin K is essential to the normal formation of prothrombin, it thus becomes an integral factor in the process of blood clotting.

Perhaps the underlying factor in reducing "surgical mortality" is the management of the body fluids, the replacing of electrolytes and of serum and blood when needed and the avoidance of alkalosis. The work of Coller and others is outstanding in this field.

The use of the Wangenstein tube has become universal and is often life saving in combating postoperative regurgitation, vomiting and distention. It has practically superseded high enterostomy, which some years ago was often performed to alleviate these symptoms.

The administration of oxygen in high concentration in the oxygen tent after operations on the gallbladder permits the patient to breathe more easily, prevents distention and is thought to guard against pneumonia.

In the matter of operative technic there has been steady progress. Gentleness in handling tissues and sharp, clean dissection have become more widespread among surgeons. Clear visualization of the bile ducts before clamping or dividing them has become general, as has knowledge of their anatomic variability.

It was not uncommon thirty years ago to see a gallbladder literally ripped from the liver, leaving a bleeding and easily infected area. Today, with subperitoneal removal, the bed of the gallbladder on the liver is left dry, smooth and clean.

However, the surgeons of 1910 were not lacking in merit or skill. One of Halsted's last contributions was the idea of exploring and draining the common duct through the stump of the cystic duct. It is a technical maneuver which has not met the acceptance which it deserves.

The methods of managing fistulas and strictures of the ducts have definitely improved.

Fortunately for patients and surgeons, the spa treatment of disease of the biliary tract practically does not exist in America, and consequently one does not encounter so many cases of advanced peribiliary involvement, such as severe chronic pancreatitis, hemorrhagic pancreatitis, chronic hepatitis and internal fistulas.

Many surgeons today are looking at acute cholecystitis in the light of acute appendicitis and are advising and performing immediate

operation. Nevertheless, the analogy is not complete, for the gallbladder rarely perforates. In a series of 350 cholecystectomies performed by me, only 1 gallbladder showed macroscopic perforation, and that occurred in a neglected diabetic patient of 72. Lahey stated that in a series of more than 1,800 cases he encountered no rupture of the gallbladder. Certainly, the early recognition and surgical treatment of these conditions prevent the advanced pathologic conditions seen in European clinics, which is reflected in an improved morbidity and mortality rate.

Not the least among the advantages enjoyed by the surgeon of today is that of modern anesthesia. Recently, the application of drugs of the sulfanilamide group to the treatment of peritonitis has shown remarkably good results, and this holds great promise. Doubtless the next thirty years will bring forth many advantages which are not on the horizon of today.

# THE HUMAN SIDE OF SURGERY

J M T FINNEY, M D

Professor Emeritus of Surgery, the Johns Hopkins University  
BALTIMORE

In these ultrascientific days it may possibly be construed by some as rank heresy even to suggest that there may be something else in surgery besides the purely scientific aspect. I yield to none in my admiration for those devoted men and women who have dedicated their lives and their all to science and to research into the hidden mysteries of nature. All honor to them, and may continued success attend their labors! Humanity has greatly benefited by their invaluable contributions to the sum total of human knowledge.

With no thought of detracting one iota from the credit due them, I feel constrained, however, to draw the attention of the members of the medical profession to a matter of prime importance in this connection. I believe that it will be generally accepted as a matter of common experience that as a surgeon grows older and sees more of life, particularly of the lives of his patients, and becomes better acquainted with the effect, both physical and mental, of a surgical operation on the patient, he becomes more philosophically inclined. He becomes less apt to operate by rote, as it were, and more inclined to consider each case as an individual entity and each patient as a human being just like himself and not as just one more subject to be operated on. He will, to be sure, give his patient the benefit of all that science has taught in the way of modern aseptic surgery, but even all this will not suffice for a thoughtful, observant, experienced surgeon. He will have learned after years of careful observation that there is something more in surgery than the mere mechanical carrying out of all the minute details required by the present day conception of aseptic technic, that in order to secure the best results due regard must be paid to the human element involved. It must never be forgotten that the surgical operation is being performed on a human being, whose feelings and emotions must be duly considered.

Physiologists—Cannon, Freeman, Howell and others—tell of the marked effect that emotional disturbances, such as fear or rage, may exert on the bodily functions, so marked, in fact, at times as to constitute a real menace to life itself. From the days of Hippocrates to the present time physicians have been taught that in order to secure good healing of wounds it is necessary to remove or to lessen as far as possible the effect of all factors that may exert a deleterious influence on this process. Every surgeon of experience knows how much better, as a rule, wounds heal in persons at peace and rest in mind and body. There can be little

doubt, therefore, that the state of mind in which the patient approaches an operation exerts a real influence for good or evil on its outcome. I have elsewhere called attention to the fact that a patient who, to use a common expression, is "scared to death" or who is greatly worried by gloomy forebodings as to the result of the operation or who has made up his mind that he is surely going to die is in a much less favorable condition to undergo a serious surgical procedure and make a satisfactory recovery therefrom than is one whose apprehensions and emotions are not all stirred up. As I acquire wider experience, I am more and more impressed with the advisability of the operating surgeon's paying greater attention to the mental state of the patient about to be operated on. Of course, it takes time and trouble to do this, and the surgeon's time is limited and valuable as well, so much so that he is unable or, more likely, unwilling to give up much of it to talk to and to reassure nervous or apprehensive patients concerning the nature and probable outcome of the proposed operation.

I am becoming all the time more and more convinced that it is not enough simply to inform a patient in a casual, matter-of-fact way that on a certain day at a certain hour he will be operated on and to let it go at that. The ideas current in the lay mind with regard to the discomforts, dangers and possibly unsatisfactory results inseparably connected with a surgical operation are often so erroneous and so terrifying as to constitute a real menace to the success of the operation, to say nothing of the needless mental suffering entailed. The careful, conscientious surgeon will, therefore, before undertaking any operative procedure, be sure to take the time to satisfy himself that his patient is properly informed as to just what it is proposed to do and why and also, as far as it is humanly possible to foretell, just what it is hoped to accomplish. In this way only can the degree of confidence and cooperation necessary to the fullest measure of success be established between the surgeon and the patient. But some one will say "I haven't the time. I can operate on but half the number of patients that I do now if I spend so much time with each individual patient." The answer is simple and sure. No surgeon has the moral right to undertake to do more than he can properly accomplish.

The salutary effect that entire confidence in his physician or surgeon exerts on a patient is a matter of common knowledge and remark. Who has not met with instances in which the whole aspect of a case has been quickly changed by the effect on the morale of the patient that renewed confidence inspires? On the other hand, lack of confidence in one's physician or surgeon creates an atmosphere of suspicion and distrust which is most unfavorable to a satisfactory outcome of any prescribed course of treatment, whether medical or surgical. As a result of these observations, I have become impressed with the fact on which I wish to lay especial emphasis, that in preparing for a surgical operation there

is something more to be taken into account than merely the diagnosis, the aseptic technic, the administration of the anesthetic and the use of the knife, vitally important as all of these are—namely, the state of mind of the patient at the time of the operation

It is hoped that this brief paper may direct the attention of those members of the medical profession to whose notice it may come to a phase of surgery which has hitherto not received the attention which its importance deserves, namely, the human element. Every one will agree that the surgeon has no more right to inflict needless mental anguish than he has to cause unnecessary physical pain. Both tend to lower the resistance of the patient and so render him a less favorable surgical risk. Therefore, one of the first obligations of the surgeon when he assumes the responsibility of the care of a patient is to acquaint himself with, and to remove as far as is humanly possible, all obstacles physical and mental, to a successful conduct of the case. In order to do this satisfactorily it is essential that the surgeon should come to know as intimately as possible what the old family doctor used to call "the constitution" of his patient. Until quite recently it was customary in some circles to smile complacently when this expression was used. Now, however, its true significance is beginning to be more generally recognized.

In spite of the fact that every one who knows anything about the healing of wounds is aware of the fundamental nature of the facts just stated, how much attention does the average surgeon in his busy life pay to them? To be sure, ordinary care is usually exercised to keep the patient quiet and to relieve unnecessary pain, but that is all. Experience, however, will show that time taken to gain the patient's confidence, to remove doubts and tears from his mind, to explain just what it is proposed to do and why and what the chances of recovery of health and bodily functions are is time well spent and will yield rich returns in peace of mind, better wound healing and more rapid and complete convalescence. The *sine qua non* of the accomplishment of the best in surgery is attention to detail, mental, physical and technical. It is nothing short of the best that the surgeon should strive after in his work, it is not sufficient that it should be "good enough." In the hundredth case that the surgeon should be constantly striving and preparing himself to meet. This is the case the successful man, the man of which will tax the resources of the surgeon to the utmost. Ninety-nine will probably take care of themselves either because of (horrible thought) perhaps even in spite of whatever the surgeon may do.

Finally, in all professional efforts let there be no whit less scientific, but more of the human, element—more heart in all the surgeon's relations with his patients. They will thus care less and he will have more real satisfaction in his work.

# INTRATHECAL ADMINISTRATION OF TETANUS ANTITOXIN

WARFIELD M. FIROR, M.D.

BALTIMORE

The treatment of clinical tetanus is in an uncertain and unsatisfactory state. The mortality is high, there is no agreement as to the form of treatment that gives the best results, and the therapeutic use of antitoxin has not brought about an appreciable decrease in the death rate. The explanation commonly given for this therapeutic failure is that tetanus antitoxin cannot neutralize toxin which has become fixed by the tissues. It is impossible to verify this statement in human beings, but with dogs Abel and his associates have thrown some light on the fate of tetanus toxin in the body<sup>1</sup>. They have shown that up to a certain time one or more lethal doses of toxin which are apparently fixed can still be neutralized if considerable excess of antitoxin is given, but if administration of antitoxin is delayed for too long a time the fixed toxin is not susceptible to the antitoxin. It has been suggested<sup>2</sup> that the toxin becomes altered after it is fixed in the central nervous system and that when altered it cannot be neutralized. Unfortunately, with patients there is no method by which one can ascertain (*a*) whether symptoms are due to the presence of a lethal or a sublethal amount of toxin in the body, (*b*) whether or not a lethal quantity has been fixed and (*c*) whether the fixed toxin can be counteracted by antitoxin. In treating patients, therefore, one must proceed on the assumption that a lethal amount of toxin has not become fixed and rendered unsusceptible to antitoxin.

Most physicians agree that a patient with general tetanus should be given antitoxin as soon as possible, that the wound of entrance should be widely excised even though it may appear to be well healed, that sedatives should be given and that general measures, such as rest, quiet and adequate nourishment should be provided, but here agreement stops. Some physicians still advocate treatment with phenol. There are many

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From the Surgical Hunterian Laboratory of the Johns Hopkins University

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<sup>1</sup> Abel, J. J., Evans, E. A., Jr., and Hampil, B. Bull. Johns Hopkins Hosp. 59: 307, 1936

<sup>2</sup> Firor, W. M., and Lamont, A. Ann. Surg. 108: 941, 1938.

articles on the use of avertin with amylene hydrate. Magnesium sulfate has an equally large and enthusiastic number of supporters. Some workers recommend administration of very large amounts of antitoxin, others say that large amounts are unnecessary. The question as to the best route for administration of the antitoxin causes the most controversy. Wainwright,<sup>3</sup> in 1926, stated that the quickest way to reduce mortality in general tetanus is to forbid intraspinal injection of antitoxin, and he presented statistics from which he concluded that the intravenous route is the best one. Ashhurst<sup>4</sup> criticized the interpretation of these statistics and strongly advised the use of the intrathecal method. From time to time every possible route of injection has been suggested, and statistical support has been offered in each instance.

Such divergence of opinion means that in actual practice no single method has been shown to be much better than another. This may be due to the fact that very few clinicians have had a sufficient number of patients to compare adequately the different methods. Since in patients one is unable to measure the amount and the condition (state of fixation) of the toxin, it is impossible to say whether a patient would survive regardless of the treatment employed. Furthermore, evaluation of clinical reports is made more difficult by the common failure to specify (a) the length of the incubation period, (b) the interval before treatment was begun, (c) the severity of the symptoms, (d) the details of the treatment, (e) the location of the wound, (f) the age of the patient, (g) the presence of other conditions which might have caused death and (h) the culture of *Clostridium tetani* from the wound. I have reviewed the clinical reports for the past twenty-five years and have been unable to find any basis on which to compare the results and arrive at valid conclusions. There are, however, two exceptions, those of Yodh<sup>5</sup> and Vener,<sup>6</sup> and I shall consider these in the comment at the end of the paper.

Since, therefore, the actual conditions of patients with tetanus are not accurately known, one is forced to study the disease by animal experimentation. For this paper only one of the many questions concerning general tetanus has been investigated. In combating general tetanus in a dog poisoned with two lethal doses of toxin, is the intrathecal administration of a given amount of antitoxin better than the intravenous route? It is obvious that, unlike a patient, such a dog is not continuously

<sup>3</sup> Wainwright, J. M. Tetanus. Its Incidence and Treatment, *Arch Surg* **12** 1062 (May) 1926.

<sup>4</sup> Ashhurst, A. P. C. Prognosis of Tetanus. *J. A. M. A.* **87** 2089 (Dec 15) 1926.

<sup>5</sup> Yodh, B. B. *Brit M J* **2** 589, 1932.

<sup>6</sup> Vener, H. L. *California & West Med* **48** 193, 1938.



absorbing toxin from a focus of infection, so in these experiments it is not necessary to provide a constant supply of antitoxin from repeated injections

From time to time investigations similar to those reported in this paper have been carried out with different species of animals. Recently Shumacker, Lamont and I<sup>7</sup> reviewed these experiments and commented on them. A serious criticism of much of the earlier work on this subject is that treatment with intrathecal antitoxin was started before general tetanus had developed in the animals. To nullify this criticism, we compared the efficacy of the intravenous and intrathecal routes in guinea pigs and in dogs after unmistakable signs of general tetanus were present. Although these experiments<sup>7</sup> were carried out on a small number of animals, the results seemed to indicate a real superiority for the intrathecal route. This was true in both tetanus-sensitive animals (guinea pigs) and tetanus-resistant ones (dogs). The clinical importance of this observation made it desirable to repeat our experiments on a much larger scale and to attempt to investigate the following related problems

- 1 Whether the effects of antitoxin given intrathecally are due wholly or in part to a nonspecific inflammatory reaction in the meninges
- 2 Whether antitoxin introduced into the lumbar subdural space is as efficacious as that placed in the cisterna
- 3 Whether it is possible to save the life of animals which are prone and convulsive with severe general tetanus

#### METHODS AND MATERIALS

The tetanus toxin used in these experiments was lot no 641-G from the Lederle Laboratory. The large amount of concentrated antitoxin used was supplied by Sharp & Dohme, Incorporated. The strength of the toxin was determined at intervals according to our usual method<sup>1</sup>. Lumbar punctures were made at the level of the second to the fourth lumbar segment with a shortened human lumbar puncture needle. Cisternal punctures were made with an ordinary 2 inch (5 cm), 20 gage hollow needle. In no instance was the antitoxin injected until clear spinal fluid issued from the needle. Neither intravenous nor parenteral fluid was given to the dogs which were prone, but they were fed raw ground beef, milk and water by hand. Autopsies were performed on all dogs which died.

#### EXPERIMENTS

Healthy mongrel dogs were given 900 guinea pig median lethal doses (G-P LD50's) of tetanus toxin filtrate per kilogram of body weight intravenously. This was approximately two lethal doses. Fifty-three hours later the animals were divided into groups according to the severity of their symptoms and were given 680 American units of tetanus antitoxin per kilogram, either intravenously or intra-

<sup>7</sup> Shumacker, H. B., Firor, W. M., and Lamont, A. Surgery, to be published

articles on the use of avertin with amylene hydrate. Magnesium sulfate has an equally large and enthusiastic number of supporters. Some workers recommend administration of very large amounts of antitoxin, others say that large amounts are unnecessary. The question as to the best route for administration of the antitoxin causes the most controversy. Wainwright,<sup>3</sup> in 1926, stated that the quickest way to reduce mortality in general tetanus is to forbid intraspinal injection of antitoxin, and he presented statistics from which he concluded that the intravenous route is the best one. Ashhurst<sup>4</sup> criticized the interpretation of these statistics and strongly advised the use of the intrathecal method. From time to time every possible route of injection has been suggested, and statistical support has been offered in each instance.

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<sup>7</sup> Shumacker, H. B., Firor, W. M., and Lamont, A. Surgery, to be published

cisternally The results of these injections are shown in table 1 It is obvious that intracisternal administration of antitoxin is more effective than intravenous in curing early, moderate and well developed general tetanus, for of 36 dogs treated by intracisternal injections only 3 died, whereas 19 of the 25 treated by intravenous injections died It was noted that the animals which recovered from intracisternal

TABLE 1—*Effect of the Route of Administration on the Therapeutic Efficiency of Tetanus Antitoxin in General Tetanus in Dogs\**

Symptoms at Time of Treatment with Tetanus Antitoxin	Route of Administration of Tetanus Antitoxin				No Treatment with Antitoxin	
	Intracisternal		Intravenous		No That Died of Tetanus	
	No of Animals	No That Died of Tetanus	No of Animals	No That Died of Tetanus	No of Animals	No That Died of Tetanus
Early ears erect, brows furrowed	15	1	14	8	6	6
Moderate ears erect, brows furrowed and neck stiff	10	1	2	2	1	1
Marked ears, brows and neck the same slight general stiffness	8	1	9	9		
Severe generalized stiffness but animal not prone or convulsed	6	4	3	2	2	2
Total	39	7	28	21	9	9

\* Each dog received 900 G P LD<sub>50</sub>'s per kilogram of tetanus toxin intravenously Fifty three hours later each dog treated received a single injection of 680 American units per kilogram of tetanus antitoxin

TABLE 2—*Effect of the Route of Administration on the Therapeutic Efficiency of Tetanus Antitoxin in General Tetanus in Dogs\**

Symptoms at Time of Treatment with Tetanus Antitoxin	Route of Administration of Tetanus Antitoxin					
	Intracisternal		Intravenous † Plus Horse Serum Intracisternally		Intravenous	
	No of Animals	No That Died of Tetanus	No of Animals	No That Died of Tetanus	No of Animals	No That Died of Tetanus
Early ears erect, brows furrowed	15	1	7	2	14	8
Moderate ears erect, brows furrowed and neck stiff	10	1			2	0
Marked ears, brows and neck the same slight general stiffness	8	1	9	3	9	9
Severe generalized stiffness but animal not prone or convulsed	6	4	3	3	3	0
Total	39	7	19	8	18	21

\* Each dog received 900 G P LD<sub>50</sub>'s per kilogram of tetanus toxin intravenously Fifty three hours later each dog treated received a single injection of 680 American units per kilogram of tetanus antitoxin

† The dogs in this group received the antitoxin intravenously and at the same time an equal amount of normal horse serum intracisternally

injections had little or no progression of the disease The superiority of intracisternal injections in curing severe or far advanced tetanus is not apparent in this experiment, but further investigation of this point is recorded in table 4

Dr LeRoy Fothergill, of the Harvard Medical School, suggested that the results of intracisternal administration of antitoxin may be due to the inflammatory reaction produced in the meninges by the serum In an attempt to find out whether this is true, we studied a series of dogs which received tetanus antitoxin intravenously and

an equal amount of horse serum intracisternally. The data are recorded in table 2. It is clear that the combined use of horse serum and intravenous antitoxin produced better results than did the use of intravenous antitoxin alone, but the results were not so good as those obtained from intracisternal administration of antitoxin. It must be pointed out, however, that the number of animals used in this experiment was not large, and consequently the differences are correspondingly less significant.

The purpose of our next experiment was to determine whether there is any difference between the efficiency of antitoxin given intracisternally and that given in the lumbar region. The results are tabulated in table 3 and show that within the limitations of this experiment the former route is the better one except in animals with severe symptoms.

We then tried to see whether intracisternal injections of antitoxin can save an animal with far advanced general tetanus. The results are shown in table 4. We were able to save only 1 dog in the series—a dog which received the antitoxin intracisternally. We were surprised that we could save even 1, for the amount of toxin and the lapse of time before antitoxin was given were so great that we felt certain

TABLE 3—*Comparison of Intracisternal and Lumbar Injections of Tetanus Antitoxin in General Tetanus in Dogs*

Symptoms at Time of Treatment with Tetanus Antitoxin	Route of Administration of Tetanus Antitoxin			
	Intracisternal		Subarachnoid (Lumbar)	
	No of Animals	No That Died of Tetanus	No of Animals	No That Died of Tetanus
Early ears erect brows furrowed	15	1	5	2
Moderate ears and brows the same neck stiff	10	1	15	2
Marked ears brows and neck the same slight general stiffness	8	1	1	1
Severe general stiffness no convulsions	6	4	4	3
Total	39	7	25	8

that nothing could save the animal. It is interesting that animals given intracisternal injections survived appreciably longer than those given intravenous injections. The observation that we were able to save 1 dog with advanced general tetanus offers real encouragement in the treatment of patients critically ill with tetanus. The result of treatment in this 1 dog is not necessarily inconsistent with our view that when a lethal amount of toxin has been fixed and altered no amount of antitoxin avails to save the animal's life, for Abel has shown that severe symptoms of generalized tetanus may occur when sublethal amounts of toxin are given. It is likely that when treatment was begun for this particular dog a lethal quantity was not yet fixed in the central nervous system. This experiment is of sufficient importance to justify a brief account.

Each dog received one lethal dose (480 G-P LD<sub>50</sub>s per kilogram) of tetanus toxin intravenously. As the dogs became prone and exhibited frequent convulsions they were assigned alternately to one of three groups. One group received antitoxin intracisternally, one group received antitoxin intravenously, and the third group received no antitoxin. The animals in the first two groups were given 1,300 units of antitoxin per kilogram at each injection. If the animals survived, these injections were repeated at approximately twenty-four hour intervals to a total of five.

In table 5 we have summarized all the antitoxin experiments carried out on dogs in our laboratory. This table includes animals which were given 480 to 2,400 G-P LD50's of toxin per kilogram. They were treated at various stages of the disease (from forty-eight to one hundred and sixty-eight hours after introduction of the toxin). Some animals received as little as 1 unit of antitoxin per kilogram, whereas

TABLE 4—*The Treatment of Advanced General Tetanus in Dogs*

Route of Administration of Tetanus Antitoxin	Number of Dogs	Number of Deaths	Average Time of Death in Hours	
			After Injection of Toxin	After Onset of Symptoms
Intracisternal	4	3†	163*	41*
Intravenous	4	4	145	22.6
Control—no tetanus antitoxin	5	5	124	80

\* The animal which survived is not included in these figures.

† A brief protocol of the surviving animal follows:

March 12, 11 a. m. Received toxin (2,500 G-P LD50's)  
 14 Beginning erection of ears  
 16, 11 a. m. Trismus, stiff body, questionable distemper  
 6 p. m. Prone, clonic convulsions, received 67,600 American units of antitoxin intracisternally  
 18, 10 a. m. Condition the same, received same dose of antitoxin  
 19, 10 a. m. Condition the same, received same dose of antitoxin  
 20, 11 30 a. m. Condition the same, received same dose of antitoxin  
 21, 10 30 a. m. Condition the same, received same dose of antitoxin  
 22 No longer having convulsions, can drink, still prone and stiff, has external opisthotonos. The dog gradually recovered.

TABLE 5—*Effect of the Route of Administration on the Therapeutic Efficiency of Tetanus Antitoxin in General Tetanus in Dogs\**

	Route of Administration of Tetanus Antitoxin				No Treatment with Antitoxin
	Intra-cisternal	Sub-arachnoid (Lumbar)	Intravenous Plus Horse Serum Intra-cisternally	Intra-venous	
Total number of animals	70	30	20	65	21
Number of deaths	24	11	9	52	21
Number of animals that died of tetanus	17	11	8	47	21
Number that probably died of tetanus, although other pathologic conditions were present	2		1	2	
Number that died of other causes, having had no progression of the tetanus	5			3	
Gross mortality	34%	37%	45%	80%	100%
Mortality from tetanus	27%	37%	45%	75%	100%

\* The dogs received from 480 to 2,400 G-P LD50's per kilogram of tetanus toxin intravenously. The dogs treated received from 1 to 2,400 American units of tetanus antitoxin at intervals of from 48 to 168 hours after the injection of the toxin.

the maximum amount given was 2,400 units per kilogram. It will be seen that if one excludes animals dying from other causes than tetanus, the mortality in the 70 dogs which received the antitoxin intracisternally was 27 per cent. In the 30 dogs treated by lumbar injection the mortality rate was 37 per cent. In the 20 dogs given antitoxin intravenously and horse serum intracisternally the death rate was 45 per cent, and in those treated solely by the intravenous route the mortality rate

was 75 per cent. All the animals not treated died of tetanus. According to these figures the superiority of the intrathecal route is not so great as it is in the treatment of dogs suffering from early and moderately severe tetanus, yet they furnish conclusive evidence that the mortality among dogs dying from general tetanus is lowest when the antitoxin is administered intracisternally.

#### COMMENT ON CLINICAL REPORTS

Clinicians have been sharply divided as to the desirability of giving tetanus antitoxin intrathecally. Wainwright,<sup>8</sup> Gage and DeBakey<sup>9</sup> and many others have advised against its use. Golla<sup>10</sup> and Calvin and Goldberg<sup>10</sup> stated that no conclusions can be drawn from their experience as to whether subdural injection of antitoxin is better than other methods of treatment. Many authors have strongly advocated this form of treatment. Recently Vener<sup>6</sup> has described 75 consecutive patients treated with intracisternal injections, with a gross mortality of only 26.6 per cent. When he omitted the patients who died within twenty-four hours after admission to the hospital, the mortality was only 16.6 per cent. It is difficult to derive sound conclusions from the clinical reports as to the best method of treatment, for the groups treated in the various ways are not capable of being compared. Frequently authors have failed to specify the length of the incubation period, the interval before treatment, the severity of the disease when treatment was begun and the details of the treatment. Besides the encouraging report of Vener, there has been published a paper of particular significance by Yodh, who treated 214 patients with tetanus in a group of 263 who were seen during a relatively short period. He divided these patients into three groups and presented evidence to show that they were approximately the same with reference to the length of the incubation period, the absence or presence of a history of injury and the presence of a septic wound. In the first group, 49 consecutive patients received small doses of antitoxin (20,000 units) intravenously or intramuscularly. Three of these patients also were given "lumbar subarachnoid injections." In this group there was a gross mortality of 77.5 per cent, which was lowered 10 per cent when those patients who died within twenty-four hours after admission were excluded. In the second group, 102 patients were given larger doses of antitoxin (averaging about 40,000 units) by the intravenous or the intramuscular route. The gross mortality was 65 per cent, and when the patients who died within twenty-four hours after admission were omitted, this rate fell to 50 per cent. Finally, the last 112 patients received the same amount of antitoxin as those in the second group, but

<sup>8</sup> Gage, M., and DeBakey, M. *South Surgeon* 4 246, 1935

<sup>9</sup> Golla, F. *Lancet* 2 966, 1917

<sup>10</sup> Calvin, J. K., and Goldberg, A. H. *Prognosis of Tetanus*, J. A. M. A 94 1977 (June 21) 1930

all of them were given it intracisternally as well as by other routes. The gross mortality was 46.5 per cent, and when the patients who died within the first twenty-four hours were left out this figure fell to 23.4 per cent.

Recently Dietrich<sup>11</sup> has described the clinical picture of children dying from severe reactions following intravenous or intracisternal injections of antitetanic serum. He stated that "it resembles certain phases of bulbar poliomyelitis, or some other disease with medullary pressure or edema." In none of our animals has such a reaction occurred, nor has Vener reported fatal reactions in any of the 75 patients he treated by intrathecal injections of antitoxin. Dietrich's report contains no information as to the quantity of serum used, the rate of administration, the dilution of the injected antitoxin or the source of the serum. He stated, however, that "the refinement of serums in the last few years has probably aided in reducing the number of severe reactions." It is our feeling that Dietrich's observations give a timely warning against injudicious injection of antitetanic serum but that his data do not justify the abandonment of intravenous or intrathecal administration of antitoxin.

#### GENERAL COMMENT

The experiments which form the basis of this paper indicate clearly that in the treatment of dogs with mild or moderately severe tetanus intracisternal injections of antitoxin are far more effective than intravenous ones. These experiments in themselves do not warrant the use of intracisternal injections for patients, but when considered with the clinical reports of Yodh or Vener they furnish a strong argument for the employment of this form of treatment. It is highly desirable that a more refined antitetanic serum be produced in order to minimize the severe reactions described by Dietrich. This may possibly be accomplished in one of two ways. First, ordinary antitetanic horse serum may be concentrated and purified by the action of proteolytic enzymes, as has been done with diphtheria antitoxin.<sup>12</sup> Secondly, human serum containing a high titer of tetanus antitoxin may be produced by active immunization of human donors with tetanus toxoid. This possibility was first suggested, as far as I know, by Dr. Clarence Hyland, of the Serum Center of the Children's Hospital in Los Angeles. Our experiments comparing the efficacy of intracisternal and lumbar routes are suggestive but not conclusive. Had we kept the animals in a position to cause a gravitational flow of the serum to the medulla, the apparent difference in results with the two sites of injection might have disappeared. Similarly, we do

11 Dietrich, H. F. Tetanus in Childhood, with Special Reference to Treatment, *Am. J. Dis. Child.* 59:693 (April) 1940.

12 Pope, C. G. *Brit. J. Exper. Path.* 19:245, 1938.



not consider that our experiment, which was designed to evaluate the importance of the inflammatory reaction to foreign serum in the meninges, is conclusive. Additional studies with purified serum on a larger number of animals are necessary before this question can be settled.

#### SUMMARY

Experiments are recorded which show that the intracisternal injection of antitoxin into dogs suffering from early, mild or moderately severe tetanus yields far better results than intravenous injection. In animals with severe tetanus there is little difference in the results obtained by the various routes of administration of antitoxin, but the difference that occurs favors the intracisternal route.

Dr Austin Lamont and Dr Harris B Shumacker Jr assisted in the performance of these experiments.

# ORIGIN, EVOLUTION AND SIGNIFICANCE OF GIANT CELLS IN RIEDEL'S STRUMA

EMIL GOETSCH, M.D.

BROOKLYN

The occurrence of giant cells or so-called pseudo giant cells with the chronic nonspecific thyroiditis usually designated as Riedel's struma has been frequently noted since Riedel<sup>1</sup> described this disease in 1896. In his original report, however, no mention is made in the microscopic observations of the presence of giant cells. In a considerable number of subsequent reports the occurrence of giant cells in Riedel's struma has been noted, but few studies have been made with the particular purpose of determining their mode of origin and evolution, their possible function, if any, and their ultimate fate. As a result they are little understood, and various unsubstantiated views have been expressed regarding their origin and significance. The most common misconception regarding their nature is that they are foreign body giant cells possessing phagocytic properties. One unfortunate result of this assumption has been to bestow on them a significance which cannot aid in an ultimate understanding of the etiologic factors and the true pathologic processes at work in the destruction of the thyroid gland associated with Riedel's struma. Furthermore, the presence and supposed phagocytic function of the giant cells described in many previous reports have led to mistaken diagnoses of tuberculosis, syphilis and carcinoma and to consequent misdirected therapy. A recent case of Riedel's struma is presented, together with the pathologic observations in the thyroid gland, particularly as they relate to the giant cells, which were present in large numbers. It is my purpose to interpret these observations, which are similar to those previously made in a considerable number of personal cases, with the hope that the evidence submitted will clarify the true nature of the giant cells and thus eliminate one element of confusion in understanding of the basic pathologic processes at work in this disease. One should thereby approach somewhat nearer to the cause of this condition.

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From the Departments of Surgery of the Long Island College Hospital and the Long Island College of Medicine

1 Riedel, B. Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 25: 101, 1

## REVIEW OF LITERATURE

Wilke<sup>2</sup> was one of the few authors who concerned himself specifically with the origin and function of the giant cells associated with chronic nonspecific thyroiditis of the Riedel type. He noted the occurrence of giant cells supposedly produced by irritation of the colloid acting as a foreign body and described the apparent erosion of the colloid by them. At times the giant cells were described as completely encircling a globule of colloid. He expressed doubt that the giant cells are formed by coalescence of follicular cells and implied that their origin is analogous to the formation of giant cells in the prostate, which he described as follows: The follicular lining cells disappear as a result of pressure atrophy produced by the foreign body (concretions in the prostate and colloid in the thyroid), whereupon the foreign body exerts a stimulating or irritative action on the periacinar fibrous tissue with the resultant formation of giant cells. He noted that as long as the follicular lining is intact and the foreign bodies lie free in the lumen no giant cells are formed.

Creite<sup>3</sup> was influenced to regard as tuberculous the thyroid glands in 2 instances of apparently typical Riedel's struma because of the occurrence of intrafollicular epithelial giant cells not unlike those associated with Riedel's struma. In fact, he designated them as intrafollicular tubercles. This diagnosis was made in spite of freedom from tuberculosis elsewhere, the fact that the patients had completely recovered from operation and were entirely well five to five and one-half years later and the absence of necroses or typical tubercles.

A common conception has been that the giant cells are formed in response to foreign body irritation and possess phagocytic properties. Thus Reist<sup>4</sup> reported 6 cases of Riedel's struma, in 1 of which he described epithelial giant cells in contact with, or surrounding, masses of colloid in a manner analogous to foreign body giant cells. These cells were further described as sending out radiating offshoots into the colloid and thus possibly represented the beginnings of true giant cells.

Graham and McCullagh<sup>5</sup> reported 4 cases of struma lymphomatosa (Hashimoto), a condition in some respects analogous to Riedel's struma, in 3 of which they noted the occurrence of giant cells of the foreign body type which were phagocytosing not only the colloid engulfed by

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2 Wilke. Ueber Riesenzellenbildung in Thyreoidea und Prostata. *Virchows Arch f path Anat* **211** 165, 1913.

3 Creite, C. Ueber tuberkulöse Strumen. *Beitr z klin Chir* **78** 487 1912.

4 Reist, A. Ueber chronische Thyreoiditis, Frankfurt. *Ztschr f Path* **28** 148 1922.

5 Graham, A., and McCullagh, E. P. Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid (Struma Lymphomatosa Hashimoto). *Arch Surg* **22** 548 (April) 1931.

them but the epithelial cells. By means of injections of alcohol into the thyroid gland of the dog Olper<sup>6</sup> produced epithelial giant cells derived from the follicular cells and resembling those seen in Riedel's struma. He regarded them as resulting from foreign body irritation by the colloid, on which they were stated to have a phagocytic action. Joll<sup>7</sup> emphasized what he stated to be the rare presence of foreign body giant cells in Riedel's struma as compared with Hashimoto's disease and stated that the role of these cells is elimination of the colloid which cannot otherwise be absorbed.

A further view has been that giant cells are formed by fusion of epithelial cells into protoplasmic masses which have phagocytic power. Thus Kreuzbauer<sup>8</sup> reported the observation of giant cells filled with colloid and apparently formed by the fusion of epithelial cells around degenerating colloid droplets, giving thus the appearance of foreign body giant cells whose function might be that of splitting up the colloid. Lee<sup>9</sup> noted the occurrence of multinucleated giant cells in 8 of the 9 instances of Riedel's struma reported by him and stated that these giant cells had an appearance strongly suggestive of fusion of follicular epithelial cells around droplets of colloid on which they probably exerted a phagocytic action, as indicated by their assumed content of colloid droplets. In 19 cases of atrophy and fibrosis of the thyroid gland (Riedel's struma) collected from the literature from 1930 to 1937 and in 4 personal cases McClintock and Wright<sup>10</sup> reported the occurrence of foreign body giant cells to which they attributed phagocytic properties without recording evidences for this assumption. Eisen<sup>11</sup> reported from my service 7 instances of Riedel's struma in which he noted the occurrence of multinucleated cells which he designated pseudo giant cells, in apparent distinction from the true Langhans type of giant cell, which he very rarely observed. He thought he recognized two types of giant cells, one formed of a mass of colloid with desquamated cells arranged about its periphery and the other composed of a cluster of epithelial cells that had lost their cell definition and formed pseudo giant cells containing many nuclei.

6 Olper, L. Riproduzione sperimentale di cellule giganti epiteliali nelle tiroide, *Sperimentale, Arch di biol* **89** 555, 1935

7 Joll, C. A. The Pathology, Diagnosis and Treatment of Hashimoto's Disease (Struma Lymphomatosa), *Brit J Surg* **27** 366, 1939

8 Kreuzbauer, F. H. Die Thyreoiditis chronica. Ein Beitrag zur Kenntnis der Riedelschen "eisenharten Struma," *Arch f klin Chir* **163** 86, 1930

9 Lee, J. G. Chronic Nonspecific Thyroiditis, *Arch Surg* **31** 932 (Dec.) 1935

10 McClintock, J. C., and Wright, A. W. Riedel's Struma and Struma Lymphomatosa (Hashimoto), *Ann Surg* **106** 11, 1937

11 Eisen, D. Riedel's Struma, *Am J M Sc* **192** 673, 1936

## REPORT OF A CASE

F A, an American housewife aged 52 (fig 1), was admitted to the Long Island College Hospital Dec 4, 1939, complaining of enlargement of the neck and a feeling of tightness of the throat, nervousness, tremor and easy fatigue. She was the mother of two healthy children. Her general health had always been good. She had had amenorrhea since oophorectomy and partial hysterectomy performed four years prior to entrance. During the six years prior to her admission to the hospital she had been subject to attacks of sneezing and lacrimation due to some form of allergy. Fifteen years before entrance she was told that she had an enlargement of the thyroid affecting principally the right side. She was treated with iodine, with some apparent benefit. At the same time she suffered with nervousness. During the succeeding years her nervous condition improved, but



Fig 1—Photograph showing fulness of the neck due to diffuse enlargement of the thyroid gland (Riedel's struma)

she was always cognizant of a "lump" on the right side of her throat. A tickling hacking cough, some huskiness of the voice and considerable clearing of the throat had been noted for a number of years. At no time had she suffered pain in the region of the thyroid, and there was no difficulty in swallowing. There had been occasional periods of transient aphonia after considerable use of her voice. Slight edema of the eyelids was often noted, but there was no protrusion of the eyes. A tremor had been noted for five or six years. There was no family history of goiter. The menses began at the age of 13 years and were always normal. The bowels were constipated. During the year previous to examination she was particularly conscious of nervousness, irritability and throbbing of the heart. Her greatest weight two years prior to examination was 186 pounds (84.5 Kg). Her weight on admission was 168 pounds (76 Kg), the loss of 22 pounds (10 Kg) being

attributed largely to restriction of diet. She had paid little attention to her thyroid condition until four weeks prior to admission, when she suffered an attack of "grip and head cold," after which the swelling in her neck enlarged and became definitely tender. She became fatigued more easily, and the sensation of constriction of her throat increased.

Examination showed her to be well developed and well nourished. The skin of the neck and upper part of the chest was flushed and presented a reddish, mottled appearance. A faint, wheezing "tracheal" sound was heard on deep inspiration. The eyes were bright and had a staring expression, but there was no definite exophthalmos. Slight edema of the lower lids was noted. The pupillary reactions were normal. Examination of the mouth, throat and cervical lymph glands revealed no abnormality. The neck (over the thyroid swelling) measured 34.5 cm in circumference. A diffuse, moderate prominence of the thyroid gland was noticeable, the greatest prominence being on the right side. The overlying skin was freely movable, on palpation the isthmus was found to be broadened and thickened, the lobes of the thyroid were unusually firm and resistant, moderately taut and not tender, and their surfaces were slightly uneven. The gland preserved its normal contour and appeared to be closely encircling the trachea. Discrete nodules were not felt. A slight pulse was noted over the poles of the gland, but no definite thrills or bruits were detectable. A thin, rather firm pyramidal lobe was felt. The Chvostek sign was negative. There was a slight tremor of the extended fingers. The skin was somewhat dry, and the hands and feet were cold. All reflexes were active. The pulse rate was 102, and occasional extrasystoles were noted. The temperature and respiratory rates were normal. The heart sounds were of good quality and regular. The abdomen showed a scar low in the midline but was otherwise normal. The basal metabolic rate on December 5 was +12 per cent. The systolic blood pressure registered 162 and the diastolic 120 mm. of mercury. The blood, urine and blood chemistry were normal.

The clinical diagnosis of Riedel's struma or possibly Hashimoto's disease was made. Operation was advised, and preoperative administration of iodine was omitted.

*Operation*—Removal of the isthmus and the pyramidal lobe and partial bilateral resection of the lobes of the thyroid were performed by me on December 6. Cyclopropane anesthesia was employed. A low collar incision was made, whereupon the subcutaneous tissues were seen to be unusually vascular. Dense adhesions were noted between the pretracheal muscles which, in turn, were adherent to the capsule of the thyroid gland, exposure of which was therefore somewhat difficult. The surface of the thyroid presented a mottled pinkish white appearance. A thickened isthmus and a small, firm pyramidal lobe were noted. The gland was five or six times the normal size, it was unusually firm and resistant, and the surface vessels were moderately well defined but were not elevated above the surface. Considerable extracapsular fibrosis, the fibrous tissue partially enclosing the large vessels of the neck, was noted. The thickened isthmus and a small, firm, whitish pyramidal lobe were adherent to the trachea, from which they were separated without great difficulty. On transection a creaking, gristly feeling was imparted to the hand. A bluish, thin-walled adenoma the size of a small olive was enucleated from the right upper pole. A tan nodule in the middle of the lobe and another in the lower pole gave the appearance of a circumscribed area of old gland. A restricted, partial resection of the right lobe was done, a generous residue being left toward the middle and lower portions of the lobe. A cystic cavity the size of a large pea containing hemorrhagic fluid, was encountered. Extensive areas of dense, white

fibrous tissue enclosing minute areas of light brownish gland and larger areas of atrophic-appearing gland were noted. The cut surface bled freely, requiring many fine silk sutures for the control of hemorrhage. Thereupon about one third of the left lobe was resected, a generous residue remaining. A lobulated colloid adenoma of the left lower pole, about the size of a hazelnut, was enucleated. The remaining stump was reconstructed with fine silk. A fairly large artery supplying the right half of the isthmus on the right side and the arteries at both poles of the gland appeared sclerotic. Throughout the operation there was a tendency to continuous oozing of blood from cut surfaces.

A fundamental hypersensitivity to operation, persisting from probable previous hyperthyroidism, was noted in the definite blood pressure response during operation, the systolic pressure rising to 236 mm of mercury and subsiding to 158 mm at the end of the operation. There was a mild rise in the diastolic pressure. The pulse rate in the afternoon following operation was 85. On the day after operation the highest temperature was 99.6 F. The convalescence was normal.

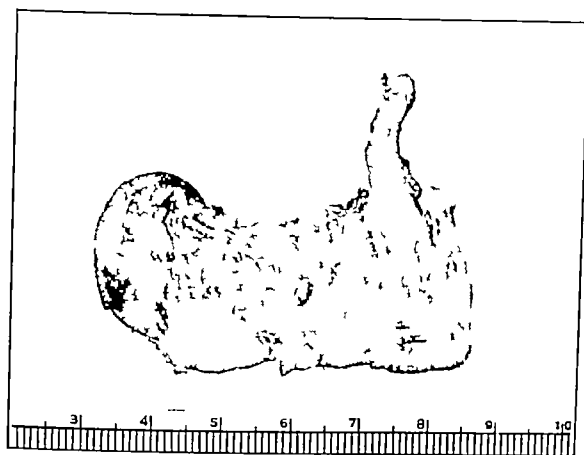


Fig 2—Photograph of the pyramidal lobe, the isthmus and the resected portion of the right lobe of the thyroid. Note the oval adenoma at the left border of the specimen.

The patient was discharged in good condition on December 16, ten days after operation. The wound was thoroughly healed. The basal metabolic rate ten days after operation was  $+3$  per cent.

*Pathologic Examination*—The tissue removed at operation weighed approximately 21 Gm and consisted of a fairly large section of the right lobe of the thyroid together with the isthmus, the pyramidal lobe and a small section of the left lobe. The larger specimen measured 5.5 by 2.5 by 2 cm. The pyramidal lobe was 2 cm in length and 0.6 cm in thickness. The resected portion of the left lobe with a margin of isthmus measured 1 by 1 by 3 cm.

*Gross Description* The resected specimen (fig 2), which was whitish, had preserved the normal surface contour of the thyroid. The thickened capsule showed superficial irregularities, the vessels were distinct, and the gland was everywhere unusually dense, firm and slightly resilient.

On the glistening, freshly cut surface could be seen broad dense bands or interlacing white fibrous tissue enclosing small irregular areas of light brown atrophic-

appearing thyroid tissue. In the center of the specimen from the right lobe there was a discrete nodule of light brown colloid thyroid gland measuring 2 by 1.5 cm in diameter, and in the right upper pole a discrete encapsulated nodule measuring 2.5 by 2 by 1.5 cm was noted (fig 2). On transection this nodule showed a thin, white fibrous capsule enclosing a gelatinous tissue consisting of small colloid cysts and distended acini. In the center of the nodule a large brownish blood clot was seen. Fibrous tissue was strikingly absent in this nodule, which presented a remarkable contrast with the dense fibrous tissue partially surrounding it. The resected portion of the left lobe presented a dense, whitish appearance and a general structure similar to that described for the right lobe. Here also small areas of tan-colored isolated islands of thyroid parenchyma and one small colloid adenoma were seen embedded in the fibrous stroma. The pyramidal lobe was firm, irregular and whitish. The left superior thyroid artery and its branch to the isthmus appeared sclerotic.

**Microscopic Description.** Sections were made from a block comprehending the entire vertical length of the resected portion of the left lobe of the thyroid. One was selected because of its characteristic pathologic features, which were representative of those in many other areas of the resected gland. The following stains and procedures were employed in the preparation of the sections: hematoxylin and eosin, Bensley's<sup>12</sup> "acid fuchsin-methyl green" method for the demonstration of mitochondria, Mallory's technic for staining fibrous tissues, and sudan III for the study of fat.

The results of low power study were as follows. Examination of the periphery of the section showed the capsule to be enormously thickened and composed of hyalinized fibrous tissue containing numerous minute blood vessels. At one end, corresponding to the upper pole of the thyroid, large, thick-walled vessels were seen. The striking feature of the section was the enormous increase in hyalinized, sparsely nucleated fibrous tissue arranged in broad anastomosing bands which divided the thyroid parenchyma into large and smaller isolated islands. The large islands appeared to be lobules of gland, and the smaller islands appeared to be the result of subdivision of lobules by the penetration of smaller strands of fibrous tissue. In the larger islands the acini varied greatly in size, from minute (with a droplet of colloid) to moderate, in the smaller islands the acinar character of the thyroid parenchyma was almost wholly lost.

The results of medium high power study were as follows. Small focal accumulations of lymphoid cells, without germinal centers, surrounding small blood vessels were noted immediately under the capsule and here and there throughout the section, particularly in the islands of isolated parenchyma. Some of the larger islands were composed of lobules of gland consisting of minute and moderate-sized acini and separated by small bands of hyalinized connective tissue. The acinar colloid was stained faintly red. The follicular lining, composed of low cuboidal or flat cells, was smooth. The nuclei were rounded, were of uniform size and contained a moderate amount of chromatin. In the relatively normal-appearing areas of thyroid tissue there was an absence of lymphoid cell infiltration, the stroma was unusually cellular, and the interfollicular small vessels were congested. The generally cellular stroma, composed of dense fibrous tissue, encircled and isolated many small islands of thyroid parenchyma hardly recognizable as such. There was a considerable increase in the interacinar hyaline fibrous tissue, which contained numbers of lymphocytes. The blood vessels were small and hardly perceptible.

<sup>12</sup> Bensley, R. R. Studies on the Pancreas of the Guinea Pig, *Am J Anat* 12: 308, 1911.



The acini, some of which were empty while others contained globules of colloid, were of small and medium size. They were lined by either flat or cuboidal epithelium or had almost completely lost their identity. Here and there in these isolated islands a few acini were seen, which appeared active in that the lining cells, provided with large, rounded, well stained chromatic nuclei, were large and low columnar, with granular protoplasm devoid of vacuoles or other evidences of degeneration. In many of the acini the large follicular cells, with pink-staining,

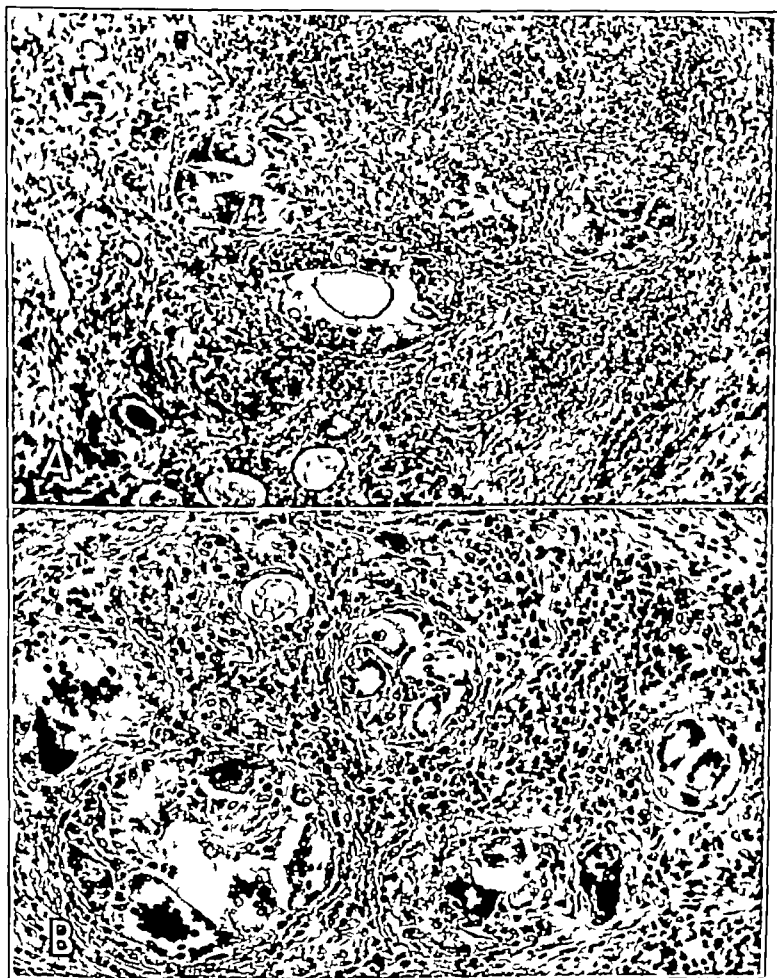


Fig 3—Photomicrographs of representative sections, *A* ( $\times 85$ ) and *B* ( $\times 150$ ), from the left lobe of the thyroid, showing desquamated follicular epithelial cells which have fused to form multinucleated, protoplasmic masses (giant cells). Various stages in progressive degeneration of the giant cells are illustrated. Note the similarity in appearance of the protoplasm of the giant cells seen in *B* and the follicular colloid shown in *A*. Only an occasional atrophic follicle remains in the cellular, fibrous stroma typical of that found in Riedel's struma. (Hematoxylin and eosin.)

granular cytoplasm, had separated from their basement membranes and were desquamating into the lumen. In this process the follicular cells had often fused into syncytial masses of granular protoplasm containing eight to ten or more dark-staining nuclei. In other acini the desquamated cells had arranged themselves around the periphery of the acinar colloid. Thus in both instances the resultant appearances simulated early stages in the formation of giant cells. In some of the acini the colloid contained discrete desquamated cells which were undergoing fatty degeneration.

The results of high power study were as follows. Islands of atrophic and degenerating thyroid follicles were demarcated by interacinar fibrous stroma in which groups of thyroid cells were still recognizable, though they had lost their acinar character. However, the striking feature was the occurrence of large numbers of medium-sized follicles, the large lining cells of which had desquamated from the basement membranes and had coalesced into definitely granular, non-vacuolated, pink-staining masses of multinucleated protoplasm. The closely aggregated nuclei were large, vesicular, round, oval or irregular and contained small amounts of granular chromatin and fairly well defined nucleoli. Occasionally the nuclei of these desquamated cells had completely circumscribed the acinar globule of colloid. In the interstices of the interacinar hyaline connective tissue there were numerous lymphoid and epithelioid cells. There were a few elongated connective tissue cells and occasional plasma cells. Rare polymorphonuclear and a few granular eosinophilic cells were seen. In the stroma between the larger acini, minute, active-appearing thyroid acini composed of cells with columnar, nonhydropic, granular protoplasm could be seen. These acini were often empty or contained a mere droplet of colloid. Other thyroid cells, in groups, had lost their follicular arrangement and appeared atrophic. The capillaries were congested and few.

The following transitional stages in the formation and degeneration of the giant cells (figs 4 and 5) could be clearly recognized: separation of follicular cells from their basement membranes and coalescence of the protoplasm and nuclei of neighboring cells into multinucleated syncytial masses, disappearance of the acinar colloid, shrinkage of the protoplasmic masses with conglomeration of the nuclei and formation of typical-appearing "giant cells", the loss of acinar identity as a result of ingrowth into the lumen of undifferentiated cells derived from the limiting fibrous membrane of the follicle completely surrounding the atrophic giant cell and finally the virtual disappearance of the protoplasm of the giant cells and karyorrhexis of their nuclear aggregates, which then were hardly recognizable in a maze of undifferentiated cells and fibrous tissue. Details of formation, degeneration and final disappearance of the giant cells were as follows.

At the beginning the follicles were partly or completely filled with pink-staining homogeneous colloid and were lined by active-appearing cuboidal cells with granular protoplasm. The nuclei were rounded or oval and densely stained (fig 4a). The colloid was often shrunken away from the lining cells.

Occasional follicles were noted in which all or the majority of the large follicular cells had separated from their basement membranes, incidentally losing their individual cell definitions. They had fallen in the lumens and thereupon, by mere accident, surrounded a central mass of colloid (fig 4b and c). The protoplasm of these rather large cells appeared finely granular and nonvacuolated, and the nuclei were rounded or oval and appeared swollen. They were relatively clear because of the small amounts of chromatin which they contained. In places the basement membrane of the follicle was devoid of cells, at other points non-nucleated protoplasmic crescents were seen still clinging to it. In some acini

where the follicular lining cells had desquamated, there was replacement by several layers of undifferentiated cells derived from the basement membrane and infiltrated between the protoplasmic masses (fig 4*d* and *f*)

Other follicles were then noted in which the desquamated cells had fused into small syncytial masses of pink-staining protoplasm containing large numbers of fine granules (mitochondria). The nuclei of these fused cells arranged themselves peripherally about masses of protoplasm, thus simulating the appearance of small thyroid acini (fig 4*e*). In some instances the compact nuclei were embedded in small, conglomerate masses of protoplasm (fig 4*f*). Central globules of homogeneous-appearing colloid were occasionally seen to be quite isolated from the adjoining masses of fused follicular cells (fig 4*c*). There was no evidence of phagocytic activity by these protoplasmic masses, which did not contain colloid droplets or cellular debris. The adjoining colloid similarly failed to give any appearance of being phagocytosed (fig 4*b* and *c*). The nuclei of the syncytial, protoplasmic masses appeared fairly large, they were rounded, oval or irregular and contained a relatively scant amount of chromatin. In several acini layers of undifferentiated nonepithelial cells had overgrown the basement membranes and were infiltrating the protoplasmic masses (fig 4*f*).

A further stage of transition was noted in the coalescence of these protoplasmic clumps into irregular, bizarre, syncytial masses containing twenty or thirty closely aggregated pyknotic nuclei (fig 5*g* and *h*). The protoplasm appeared coarsely and finely granular and without vacuoles, colloid or cellular debris. The appearance now approached that of huge giant cells (fig 5*h*, *i* and *j*). The central globule of acinar colloid, when present, appeared homogeneous, in distinct contrast with the granular protoplasm of the giant cells, which gave no appearance of phagocytosing the colloid. Often the nuclei, which were in many layers, arranged themselves in crescents bordering one side of the lumen (fig 5*j*).

In the further evolution of these syncytial giant cell masses it was noted that their protoplasm was becoming scantier but that in most instances its finely granular character was preserved. In rare instances the protoplasm contained lipid globules. The central small mass of protoplasm with peripherally situated nuclei gave the appearance of minute acini (fig 5*k*). The colloid had disappeared. The original follicles were still defined by the basement membranes, which were faintly visible (fig 5*k* and *l*). Some of these small acini were overgrown by masses of compact, undifferentiated cells with scanty, nongranular protoplasm and oval, rounded or irregular, deeply stained nuclei. This undifferentiated, nonepithelial tissue, in which the giant cells could be readily distinguished, partially or completely filled the follicle, thus incidentally surrounding the giant cells (fig 5*k* and *l*). Here again there was no evidence of phagocytic activity on the part of the giant cells, the protoplasm of which showed no inclusions of foreign material.

Other syncytial giant cell masses were then noted, in which increased numbers of fat droplets began to appear and in which shrinkage and partial disappearance of the protoplasm had occurred, with consequent coalescence of surviving nuclei into dark-staining, dense, pyknotic nuclear aggregates. From ten to thirty nuclei could be counted in a single giant cell (fig 5*j*, *k* and *l*). The nuclei were oval and atrophic appearing and contained finely granular, poorly staining chromatin. The outlines of the follicle could scarcely be recognized because the lumen had been completely filled with undifferentiated cells, embedded in which the easily recognized nuclear aggregates of the giant cells could be seen (fig 5*l*). Finally the identity of the follicles was almost or wholly lost. The giant cells at this stage were almost devoid of protoplasm and that remaining was spongy nongranular and poorly stained and contained numerous fat droplets (sudan III). The pyknotic



Fig 4—Photomicrographs ( $\times 200$ ) illustrating the gradual transitional stages in the life of the giant cells from their origin to virtual disappearance. Note the group of active-appearing follicles (a), the early swelling and fusion of adjoining cells with loss of cell definition (b), the separation of the fused follicular cells from the basement membrane and their desquamation into the lumens (c), the formation of protoplasmic masses with peripherally situated nuclei (d and e), and the concentration of undifferentiated connective tissue cells derived from the periacinar connective tissue (f).



Fig 5—Photomicrographs ( $\times 200$ ) showing the more clearly defined, multi-nucleated protoplasmic masses which assume the appearance of giant cells of various sizes and bizarre shapes (*g* and *h*), shrinkage of follicles and condensation of nuclear aggregates (*i*), crescentic massing of nuclei on one border of the lumen and overlying a mass of protoplasm (*j*) continued degeneration and shrinkage of the giant cells (*k*), and their virtual disappearance in a compact mass of undifferentiated and connective tissue cells and lymphocytes which fill the follicle (*l*). No evidences of phagocytosis of colloid or cellular debris were seen in any of the aforementioned stages

nuclei, it recognizable as separate structures, were shriveled, elongated or irregular. They contained little chromatin and showed poor staining affinity for hematoxylin. At this stage remnants of the giant cells at times appeared to lie in the stroma outside the follicles whereas in the previous stages described the giant cells had been definitely within the follicles. Undifferentiated, irregular masses of granular, chromatic material were seen, in which, at times, outlines of nuclei could be recognized. Finally the follicle was completely obliterated by the overgrowth of connective tissue. In none of these later stages were evidences of phagocytosis noted. Moreover, the stages of transition in the formation of the giant cells could be recognized in follicles in which there was no colloid or cellular debris to phagocytose (fig 5 *g, h* and *i*).

#### COMMENT AND SUMMARY

From this study of follicular degenerative changes which occur in the thyroid gland in the presence of Riedel's struma it is clear that certain conclusions which have been drawn from reported microscopic observations and which concern the occurrence, origin, manner of formation and functional significance of the so-called giant cells are in need of revision. It is essential that one be clear as to the nature of the giant cell in order better to understand the destructive pathologic processes in Riedel's struma. Two conceptions are prevalent, one a fundamental pathologic conception, the second indefinite and confusing. Thus, in one the giant cell is considered a polynucleated, syncytial mass of protoplasm possessed of phagocytic properties and derived possibly from the reticuloendothelial system, or at any rate mesoblastic in origin (MacCallum<sup>13</sup>). In the second conception it seems that any conglomerate, polynucleated mass of protoplasm, regardless of its origin or apparent function, has been designated as a giant cell, and attributes of true giant cells have been assumed. Because of lack of understanding as to the true nature of the giant cells in Riedel's struma, certain previous observers have applied to them the term pseudo giant cells without revealing just what is implied by this term. I have found few reports of microscopic observations dealing to any extent with the so-called giant cells. Often no mention is made of their occurrence. Some authors content themselves with mere mention of their occurrence, while others describe them as foreign body giant cells and assume for them phagocytic properties.

Two views have been expressed as to their origin. Thus Wilke stated the opinion that after desquamation and disappearance of the follicular epithelium the colloid remaining in the acinus acts as a foreign body irritant on the surrounding connective tissue and thus produces an irritative hyperplasia with formation of giant cells which subsequently phagocytose the colloid. A limited number of other writers have suggested that the giant cells probably arise by a process of fusion of

13 MacCallum, W. G. Textbook of Pathology, ed 6, Philadelphia W. B. Saunders Company, 1937, pp 156-160.

desquamated follicular cells As a result of studies reported here I believe that it can be stated that the origin and evolution of the giant cells are invariably anteceded by degenerative and desquamative changes in the follicular epithelial cells, which thereupon lose their cellular identity and fuse with their neighbors to form the commonly observed syncytial, multinucleated masses of protoplasm As a result of nutritional disturbances and further degeneration the protoplasm of the giant cells becomes scantier, thereby causing the nuclei of these cells to coalesce into conglomerate nuclear aggregates characteristic of the eventual giant cell It has been possible to trace unquestionable transitional stages in this process No evidence has appeared to support the view of Wilke, in fact, there are evidences to the contrary, such as the fact that the initial fused protoplasmic masses appeared before the epithelial cells had disappeared and before the lining cells had altogether left their basement membranes and had thus exposed the connective tissue to the irritative action of the colloid Furthermore, these early stages in the formation of the giant cells were visible in acini entirely devoid of colloid, which had disappeared without the assumed phagocytic action of the giant cells

The idea that these giant cells arise in response to foreign body irritation of the colloid which they subsequently phagocytose seems in the light of the observations reported here to have been incorrectly assumed by earlier authors and merely to have been accepted and repeated by subsequent investigators The basis for this assumption has been the reported inclusions in the protoplasm of the giant cells of cellular debris or colloid globules In the present studies, as also in previously observed cases, no evidences of such inclusions of either foreign material or colloid have been observed

Since, as has been shown here, the giant cells are derived from coalesced masses of degenerating, desquamated follicular cells which are in the process of destruction for probable nutritional reasons, it seems unwarranted to assume that they have a phagocytic power If this theory were correct one would be forced to assume that degenerating secretory epithelial cells have acquired the power to engulf and dissolve foreign material, a function reserved for cells originating in the reticulo-endothelial system or, at any rate, restricted to mesoblastic tissues No evidences were found of phagocytic action on the colloid, which could be distinctly differentiated from the protoplasm of the giant cells with such stains as Mallory's connective tissue stain and in the acid fuchsin method for the demonstration of mitochondria (Bensley<sup>12</sup>) Thus, with the former staining method the colloid was bright orange, whereas the giant cell was light violet or purple This differential staining would readily disclose globules of colloid, if present, in the protoplasm of the giant cells In rare instances the nuclei were grouped peripherally

about a small central mass of acinar colloid, a fact which could easily be explained by the accidental circumscription of the colloid by the follicular lining cells which had fallen into the lumen. This would further obviate the conclusion that the colloid was engulfed by the giant cell. With the technic for the demonstration of mitochondria it was found that the protoplasm of the fused masses always contained mitochondrial granules similar to those present in the follicular cells before their desquamation, whereas the colloid was always homogeneous and quite devoid of these granulations. Colloid and protoplasm were thus readily distinguishable. No homogeneous colloid bodies were seen in the protoplasm of the giant cells, and it was thus possible to contradict the occurrence of colloid globules undergoing phagocytosis. In the ordinary hematoxylin and eosin preparations confusion might readily arise because of difficulty in differentiating between colloid and the protoplasm of the giant cells due to the similarity in staining reactions and the absence of definitive demonstration of mitochondrial granules.

The giant cells were particularly numerous in the degenerating follicles occurring in the areas of densest fibrosis and consequent greatest nutritional disturbance and were never seen in the more nearly normal-appearing areas of thyroid parenchyma. This fact supports the conception that they are the result of injury followed by desquamation and fusion of follicular cells which are on the road to disintegration. They do not show the viability one would expect from vigorous, newly formed giant cells formed for the purpose of phagocytosis. The fact that they have been assumed to be foreign body cells with phagocytic properties has often rendered difficult the differential diagnosis of Riedel's struma, for their presence has led to erroneous diagnoses, such as tuberculosis, syphilis or even carcinoma, and to consequent incorrect treatment. One is forced, finally, to conclude that the giant cells are structures originally formed by fusion of desquamated follicular cells, which by gradual shrinkage of their protoplasm cause nuclear conglomerates characteristic of the late stage of giant cell formation, that they do not have phagocytic properties and that they are structures of no functional significance but are simply follicular cells on the road to destruction and disappearance in the mass of undifferentiated cells which, in the end, fill and thus obliterate the follicle. If one excludes phagocytosis by the giant cells one will approach more nearly the basic pathologic processes responsible for the destruction of the thyroid parenchyma associated with Riedel's struma.

If by the term giant cells one understands a syncytial, multinucleated mass of protoplasm derived from the reticuloendothelial system and hence mesoblastic and possessed of phagocytic properties, the designation giant cells for the multinucleated masses of protoplasm found in Riedel's struma should be abandoned. The term pseudo giant



implying, as it does, that the structure is not a true giant cell in the sense indicated, might be a more appropriate term. Multinucleated cellular aggregates is a cumbersome term but is more descriptive and is not misleading.

#### CONCLUSIONS

1 The so-called giant cells associated with the nonspecific thyroiditis designated as Riedel's struma are formed by fusion of follicular epithelial cells into multinucleated, syncytial masses of protoplasm which are desquamated into the lumen of the follicle.

2 These giant cells represent secretory thyroid cells which are on the way to destruction, as is indicated by the readily recognizable transitional stages in their progressive degeneration, final disintegration and eventual disappearance.

3 The observations reported indicate that the protoplasmic giant cell masses seen in Riedel's struma do not possess phagocytic properties as has heretofore been generally assumed and should therefore not be considered true foreign body giant cells.

4 Ultimate understanding of the etiologic factors causing the destruction of the thyroid parenchyma in cases of Riedel's struma will be advanced by realization that the so-called giant cells represent merely a first stage in the disintegration and disappearance of the thyroid epithelium. They are not causes but rather effects of the as yet obscure destructive influences operating in this disease.

# ANEURYSM OF THE DUCTUS ARTERIOSUS, WITH A CONSIDERATION OF ITS IMPORTANCE TO THE THORACIC SURGEON

## REPORT OF TWO CASES

EVARTS A GRAHAM, MD  
ST LOUIS

The remarkable development of surgery of the chest has greatly increased interest in mediastinal tumors. The removal of such tumors is now a common event. In general it has been my own custom as well as that of others to explore, with the idea of removing them, those which have not responded to roentgen irradiation, unless they are considered to be aneurysms. An unexpected experience in operating on 2 patients with aneurysm of the ductus arteriosus who did not give positive evidence of aneurysm has made me think that the experience should be recorded. This record seems especially desirable because, on the basis of these 2 cases, it would seem as if many of the features are sufficiently characteristic to make one at least suspicious of the presence of an aneurysm of the ductus arteriosus even when no pulsation can be made out. These features will be discussed later.

Although aneurysm of the ductus arteriosus itself is a rare condition, judging from the number of reported cases, it is probable that because of the great interest in thoracic tumors aroused by the modern development in surgery of the chest, thoracic surgeons will encounter the condition much more often than the scanty literature on the subject would indicate. Moreover, in addition to the cases of actual aneurysm of the ductus, there are many more cases in which an unobliterated ductus is associated with an aneurysm of the pulmonary artery. It seems desirable, therefore, that those who are interested in thoracic tumors should be aware of the existence of these aneurysms and of some of their striking characteristics.

Bronson and Sutherland<sup>1</sup> found in the literature up to 1918 only 5 cases of aneurysm of the ductus arteriosus. D'Aunoy and von Haam,

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From the Department of Surgery of Washington University and the Barrow Hospital

1 Bronson, E., and Sutherland, G. A. Ruptured Aortic Aneurysms in Childhood, with the Report of a Case, *Brit J Child Dis* **15** 241, 1918

2 D'Aunoy, R., and von Haam, E. Aneurysm of the Pulmonary Artery in Patent Ductus Arteriosus (Botallo's Duct), *J Path & Bact* **38** 39, 1934

however, in 1934 were able to collect 18 cases of aneurysm of the pulmonary artery associated with an open ductus arteriosus and they added 2 cases of their own. Costa<sup>3</sup> found that in 46.5 per cent of all patients with aneurysms of the pulmonary artery congenital defects were present and that the most common defect was a persistent ductus arteriosus (20 per cent). Recognition of the possibility of an aneurysm either of the ductus itself or of the pulmonary artery as a complication of a patent ductus not only serves to emphasize the diagnostic confusion which may arise but adds another seldom mentioned argument in favor of surgical closure of recognized patent ductus, especially since Gross and Hubbard<sup>4</sup> have demonstrated the comparative safety of such an operation.

These aneurysms in the majority of cases occur in young adulthood, but they may occur even in advanced age. In Weischer's<sup>5</sup> case the patient was 82 years old and had a saccular aneurysm of the pulmonary artery 15 cm in circumference, associated with a patent ductus. It is easy to imagine that a vestigial structure like the ductus, which probably has but little tendency to increase in size with the growth of the body, might become stretched out into an aneurysmal sac if exposed for many years to the pressure of the blood in the aorta. It is astonishing that this complication is not more common in cases of patent ductus than it actually seems to be. In the cases of aneurysm of the pulmonary artery associated with a patent ductus the most commonly proposed explanation is that the wall of the artery at the site where the aortic blood strikes it is weakened, becomes sclerosed and then yields to form an aneurysm.

#### REPORT OF CASES

CASE 1—A white man aged 31, an engineer for a gas company, was admitted to the Barnes Hospital on Dec. 16, 1936. He had been referred by Dr. James Pittman, of Houston, Texas.

He stated that for the past five or six years he had had a hacking, nonproductive cough and had noticed a slowly increasing dyspnea on exertion. About two weeks previously he had suddenly expectorated about a tablespoonful of liquid dark blood, without cough. On the next two or three mornings he coughed up sputum streaked with small amounts of clotted blood. Roentgen examination at that time revealed a mediastinal tumor. He had noticed for about a year before coming to the Barnes Hospital that he became tired easily, especially after such exercise as swimming or strenuous work.

The previous illnesses consisted of meningitis at 2 years of age, pertussis at 6 years, and operation for hernia and removal of the appendix in 1924. Physical

3 Costa, A., cited by D'Aunoy and von Haam.<sup>2</sup>

4 Gross, R. E., and Hubbard, J. P. Surgical Ligation of Patent Ductus Arteriosus. Report of First Successful Case, *J. A. M. A.* **112**: 729 (Feb. 25) 1939.

5 Weischer, P., cited by D'Aunoy and von Haam.<sup>2</sup>

examination revealed nothing important or significant except in the thorax. No abnormal heart sounds were detected. Roentgen examination of the chest showed a large rounded shadow, approximately 10 cm in diameter, projecting to the left of the aortic arch and filling the upper third of the left lung field. The aortic arch was dislocated to the right, as was the trachea. There was a dense ring of calcification which practically surrounded the tumor, which in the lateral view was seen to lie anterior to the spine and close to the anterior wall of the chest. The trachea was dislocated anteriorly by the tumor. The film taken after injection of iodized poppyseed oil showed dislocation of the trachea to the right and displacement of the bronchi of the upper lobe laterally and downward by the tumor, with none of the opaque material overlying the region of the tumor. The films of the spine showed no evidence of a destructive process involving the bony cage. The roentgen diagnosis was mediastinal tumor (dermoid cyst) with cardiac and tracheal dislocation, although it was recognized that the location of the tumor, posterior to the trachea, was unusual for a dermoid cyst.

The electrocardiogram was normal. Fluoroscopic examination showed no pulsation of the mass. Examination of the blood and of the urine revealed no abnormality. The Wassermann and Kahn reactions were negative, as was the result of a fixation test for echinococcus disease.

On December 19, with intratracheal cyclopropane anesthesia, the patient was operated on. An anterior incision in the fourth left interspace was made. The second, third, fourth and fifth costal cartilages were divided, and the pleura was entered. The upper part of the left lung was found to be rather firmly adherent to the tumor but was separated from it by dissection with the finger. The tumor itself felt very firm. It presented on its left lateral aspect an area about the size of a half-dollar which was slightly yellow and calcified. No sign of fluctuation was elicited in the tumor, and it seemed, therefore, to be semisolid rather than cystic. It was so firmly attached to the surrounding structures that it was immobile. The mediastinal pleura was dissected free from the mass on the left, but no satisfactory mobilization of the tumor could be made. Certain anatomic abnormalities were noted, such as an unrecognizable aorta. The impression was received that perhaps the tumor was a malignant teratoma which had invaded the surrounding tissues. It seemed, however, that perhaps some relief of pressure might be obtained by opening the tumor and removing its contents. Accordingly, an incision about  $\frac{1}{2}$  inch (1.2 cm) long was made in its left anterior lateral aspect. Yellowish putty-like contents bulged out of this incision. Suddenly a swishing sound was heard, caused by a terrific hemorrhage from the tumor, which was like a blow-out. An attempt was made to arrest the hemorrhage by pressure, but the tissue was so friable that the tumor was torn, and the hemorrhage could not be arrested by that method. The patient's blood pressure rapidly dropped to a point where it could not be recorded, and the heart practically stopped beating. Blood was available in the operating room, and fluid was already going into a vein in the foot. A blood transfusion was, therefore, started immediately, and 1 cc of epinephrine hydrochloride was injected into the muscle of both the right and the left ventricle. Moreover, massage of the heart was started, and in about two minutes it began to beat more forcibly. During the time that the blood pressure was very low the hemorrhage from the tumor had practically ceased. A hasty exploration with the finger revealed that there was almost certainly an aneurysm. Mattress sutures of no. 2 chromic catgut were passed rapidly through

the tumor in an effort to control the hemorrhage. This was successful, and as a result of the transfusion of 500 cc. of blood together with 500 cc. of dextrose and acacia the patient's blood pressure returned to 170. It seemed that his condition was entirely satisfactory, and the wound in the chest wall was being closed in the usual way, when suddenly his respiration ceased, and within about one minute his heart stopped beating. Efforts to revive him again by the same methods were this time unsuccessful, although there had been no hemorrhage in the meantime. It was suspected that the patient probably had emboli to the respiratory and cardiac centers. Death occurred on the table.

The anatomic diagnoses at autopsy were as follows: (1) right aortic arch with the left subclavian artery as the last main vessel coming from the arch, (2) aneurysm of the partially obliterated ductus arteriosus, (3) recent thoracotomy wound on the left, with incision and suture of the wall of the aneurysm, (4) left



Fig 1 (case 1)—*A*, anteroposterior film. The calcified periphery of the aneurysm is plainly seen. *B*, lateral view, slightly retouched to show the position of the trachea in relation to the aneurysm.

hemothorax, (5) collapse of the left lung, (6) embolus in the right vertebral artery adjacent to its junction with the left artery, (7) multiple small hemorrhages in the myocardium, (8) moderate hypertrophy of the left ventricle, (9) pulmonary edema, (10) patent foramen ovale, (11) old right inguinal operative scar.

*Pathologic Examination*—A large tumor was observed occupying the apex of the left pleural cavity, pressing into the root of the neck and compressing the upper lobe of the left lung downward and backward. Medially the tumor pressed against the trachea and caused it to deviate slightly to the right. Instead of passing anterior to the trachea and dipping down behind the left bronchus the aorta passed to the right and behind the trachea and esophagus and then followed its normal course along the vertebral column. It was also noted that the first main artery to come off the arch was the left internal carotid. After removal of the thoracic organs it was seen that the large tumor was attached to the

arch at the level at which it became continuous with the thoracic aorta. The tumor was roughly spherical, with indentations at points where resistance had been encountered. Three diameters were measured and were recorded as 11, 8 and 7.5 cm, respectively. The tumor had a somewhat rubbery, elastic feel and a covering which was formed of a thin plate of irregularly calcified tissue. Posteriorly and medially the tumor had rested on the bodies of the upper thoracic vertebrae, and here it showed a slight indentation. The bodies of the thoracic vertebrae had been noticeably eroded by the pressure of the tumor.

The aorta was opened along its lesser curvature, and there was a circular opening 2 cm in diameter which communicated directly with the tumor mass.



Fig 2 (case 1) —Photograph of the autopsy specimen. The large mass above the left lung and next to the trachea is the aneurysm. The abnormal position of the aorta on the right side is clearly seen. For evidence that the aneurysm involved the ductus arteriosus, see the text.

This opening had rounded, smooth margins covered with endothelium but quickly passed into a large cavity filled with an old laminated, partially broken up blood clot. The opening lay just below the exit of the left subclavian artery from the arch. The subclavian artery coursed up along the anterior surface of the tumor to enter the root of the neck, but, although it was closely adherent to the tumor, it did not communicate with it. The intimate connection to and direct communication with the aorta plus the character of the tumor wall and its contents clearly indicated that this was an aneurysm. An attempt was made to determine the origin of the aneurysm.

The aorta arose in the normal manner from the left ventricle, but the arch was formed chiefly by the right arch instead of the left arch. The left arch had disappeared except for the very small segment to which the left subclavian artery was attached (fig 2). The right arch, which normally drops out in embryonic life, was retained in its entirety. The left common carotid, right common carotid and right subclavian arteries arose in that order from the right aortic arch. The pulmonary artery left the right ventricle in the normal manner and divided into the right and the left pulmonary artery. On the anterior superior surface of the proximal portion of the left pulmonary artery was the small, partially obliterated stump of the ductus arteriosus. This stump had been severed either at operation or at autopsy and appeared as a short fibrous cord arising from the wall of the pulmonary artery. However, if the tumor was placed in the position it had originally occupied the fibrous cord was shown to lie adjacent to a small sacculaton arising from the tumor. At the apex of this small sacculaton there was a

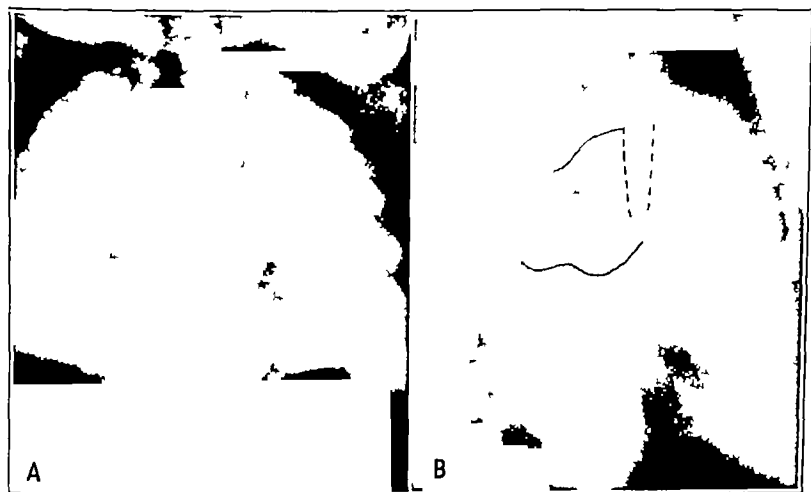


Fig 3 (case 2) —*A*, anteroposterior laminogram *B*, lateral laminogram. The aneurysm and the trachea have been retouched to show more plainly the position of the aneurysm as posterior to the trachea.

fibrous nodule which corresponded to the fibrous cord arising from the pulmonary artery. The apex of the sacculaton was cut off, and a short tube was observed about 5 mm in diameter, leading directly into the aneurysm. From these observations the conclusion was reached that the aneurysm involved the ductus arteriosus. The pulmonary arterial end of the ductus was obliterated and was represented merely by a fibrous cord. However, this fibrous cord shortly opened up into a definite tube, which was about 1 cm long and which entered a large saccular aneurysm. This aneurysmal sac in turn communicated with the arch of the aorta just below the exit of the left subclavian artery and in the region where the ductus arteriosus had communicated with the aorta in fetal life. The conclusion, then, that this was an aneurysm of the ductus arteriosus was inescapable.

The heart was of normal size and none of the chambers appeared dilated or hypertrophied. The foramen ovale was open but a septum was present which

practically covered the opening. There was no patent intraventricular septum, but the septum was very thin. In the left ventricular myocardium there were several small areas which were hemorrhagic and had a soft feel. No blocks were observed in the larger divisions of the coronary vessels, but it was thought that these areas might represent early infarction caused by emboli in the small branches of the artery. The coronary vessels showed no sclerosis. There were no lesions of the endocardium or of the valve cusps.

CASE 2—A white man aged 27, a miner, was admitted to the Barnes Hospital June 12, 1939. The chief complaints were wheezing spells, shortness of breath

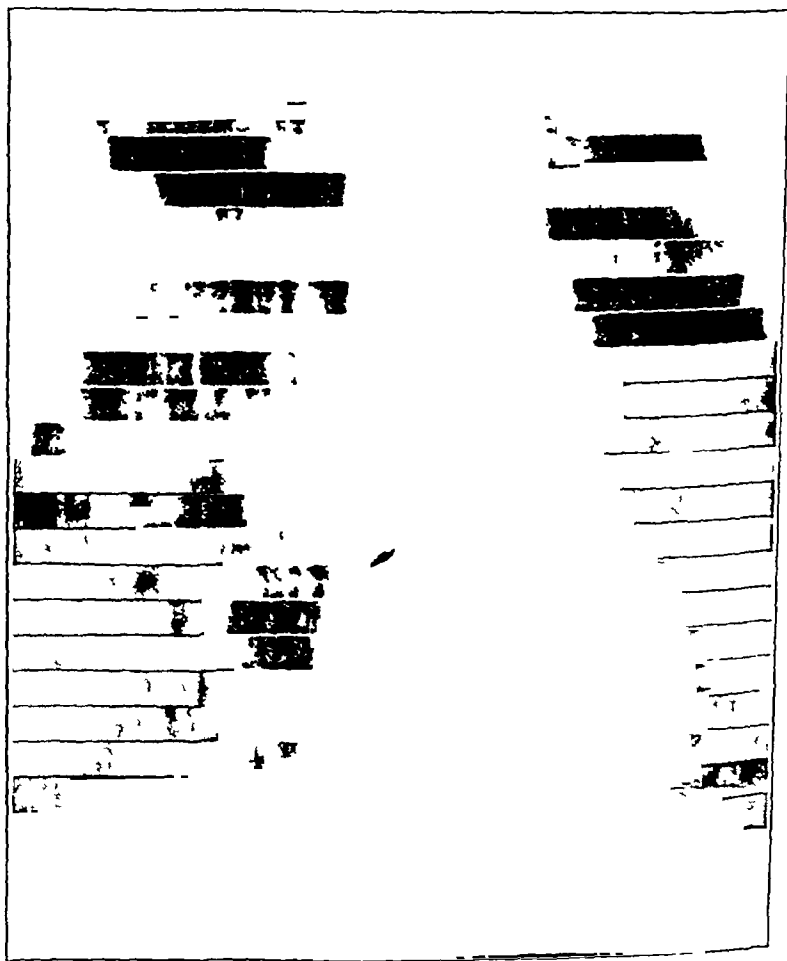


Fig 4—Roentgenkymogram which was interpreted as not showing the expansive pulsation of the tumor

on exertion and cough following exertion. He was inclined to date all his trouble from an automobile accident seven years ago, as a result of which he lost several teeth, bruised his knees and received a blow on the chest. He was not told, however, that any ribs were fractured as a result of the accident. About two months later his mother noticed that he wheezed after exertion. This had gradually increased to such an extent that he was not able to work or to do anything which required exertion. Occasionally he had a strangling sensation. Otherwise he had no complaint, and his general appearance was that of a normal young man.



*Examination*—The only significant features revealed by the examination were those concerned with the thorax, particularly the roentgen picture. The patient was examined with ordinary films, with Potter-Bucky films, with roentgenkymograms and finally with laminograms (figs 3 and 4). Overlying the upper border of the heart at the level of the pulmonary conus was a rounded, pedunculated mediastinal tumor which lay anterior to the spine and posterior to the trachea. The pedunculation of the tumor seemed particularly evident in the lateral laminogram, and the pedicle seemed to be attached to an intervertebral arch. The heart was within normal limits. The pulsation which was noted in the tumor was considered on the basis of the roentgenkymogram to be transmitted rather than expansile. No abnormal heart sounds were heard. The diagnosis from the electrocardiograms was sinus bradycardia with auricular premature beat. The pulse rate was 70. The blood pressure was 133 systolic and 83 diastolic. The blood count, urinalyses and determinations of the values for blood sugar and urea nitrogen revealed no abnormality. The Kahn reaction was negative. The vital capacity was 4,350 cc.

Because of the apparent pedicle of the tumor and the fact that no expansile pulsation was seen it was felt that the most probable diagnosis was tumor of the posterior part of the mediastinum, perhaps neurofibroma.

At operation on June 15, a posterior thoracotomy was made by elevating the scapula and dividing the posterior portions of the fourth, fifth and sixth ribs. In the arch of the aorta a tumor about the size of an orange was seen, filling the entire concavity of the arch of the aorta. The tumor was clearly wedged in between the aorta and the pulmonary artery. The mass seemed to pulsate synchronously with the aorta. It was felt, therefore, that it must be an aneurysm. In order to prove the diagnosis a small needle on a hypodermic syringe was inserted into the mass, and arterial blood was withdrawn readily through the needle. Because the aneurysm was in the anatomic location of the ductus arteriosus and because of the similarity of this case to case 1 it was felt that the aneurysm was one of the ductus arteriosus. For fear of rupturing the sac no further dissection was carried out, and the thoracotomy wound was closed without drainage.

The patient recovered satisfactorily from the operation. Information received from him seven months later stated that his symptoms were about the same as before the operation.

*Comment*—It is realized, of course, that positive proof that the aneurysm in this case originated in the ductus arteriosus is lacking without the demonstration of an opening of the ductus into the sac. On the other hand, the diagnosis seems to be the most probable one. The question as to whether the automobile injury seven years previously had anything to do with creation of the aneurysm seems to me relatively inconsequential. If the patient had a patent ductus arteriosus at the time of the injury it is not unlikely, perhaps, that trauma to the wall of the ductus might have hastened the development of the aneurysm. On the other hand, it would seem unlikely that so insignificant a trauma as one which failed to fracture any ribs would have resulted in a sufficient injury to the aorta itself to cause an aneurysm of the arch.

## GENERAL COMMENT

In retrospect, on the basis of these 2 cases it would seem that certain common findings stand out as features which would strongly suggest the possibility of an aneurysm of the ductus arteriosus. The most important diagnostic feature is the location of the tumor in the superior mediastinum, in the region of the pulmonary conus and lying posterior to the trachea. On the other hand, the more common varieties of mediastinal

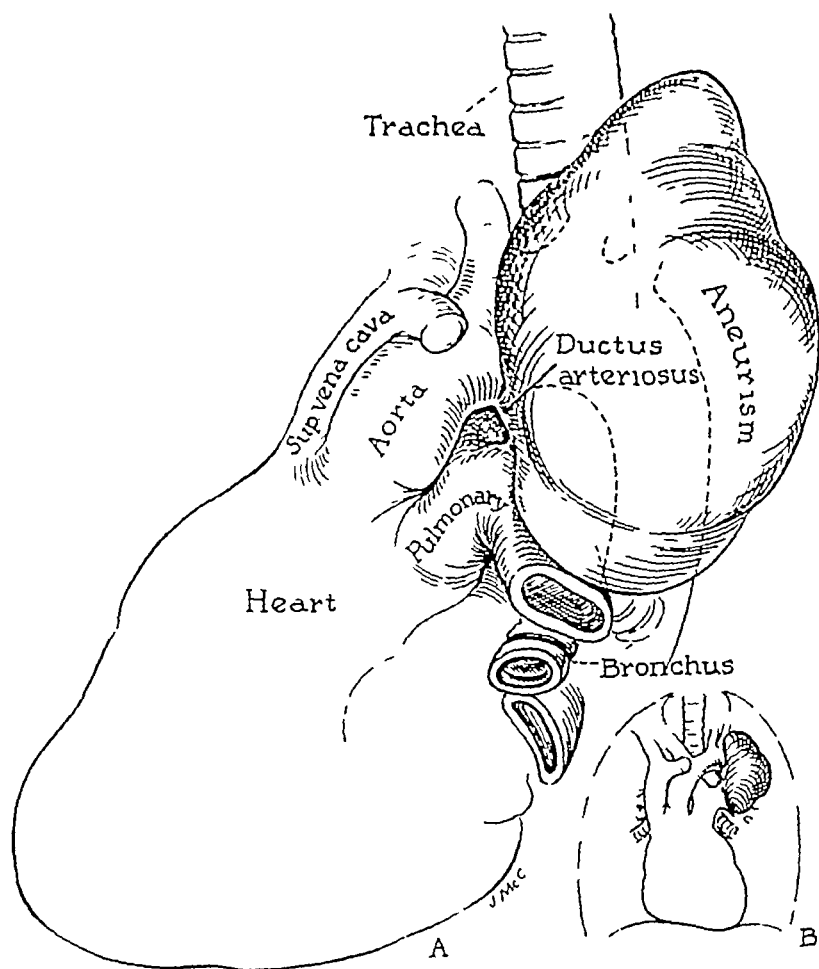


Fig 5—Diagram reconstructed in case 2 to show the mechanism of position of aneurysms of the ductus arteriosus posterior to the trachea. The large drawing is a lateral view. The inset is an anteroposterior view. An aneurysm of the ductus pushes itself out between the pulmonary artery and the aorta to assume a left lateral and posterior position.

tumor are seldom found in this location. Dermoids and teratomas are usually tumors of the anterior mediastinum, likewise, although thymic tumors and those which arise in the lymph glands (lymphosarcoma and Hodgkin's disease) are most often found in the superior mediastinum, they are not located so nearly in the region of the pulmonary conus as

are aneurysms of the ductus arteriosus. On the basis of probability, therefore, a tumor posterior to the trachea in the region of the pulmonary conus should be suspected of being an aneurysm of the ductus arteriosus or of the pulmonary artery (fig 5). Absence of recognizable expansile pulsation even in roentgenkymograms and of abnormal heart sounds is of no significance, as the 2 cases reported here illustrate. It was astonishing to me that neither patient gave evidence of a disturbance of the left recurrent laryngeal nerve. Moreover, I do not find this complication mentioned in the literature. Probably in most cases an exploratory thoracotomy is advisable. It may perhaps be predicted that some day an aneurysm of the ductus arteriosus will be found small enough to permit excision.

# STERILIZATION OF THE AIR IN THE OPERATING ROOM WITH BACTERICIDAL RADIATION

RESULTS FROM NOV 1, 1938 TO NOV 1, 1939, WITH A FURTHER REPORT AS TO SAFETY OF PATIENTS AND PERSONNEL

DERYL HART, M.D.

DURHAM, N. C.

As interest in the use of ultraviolet rays of certain wavelengths as an agent for killing micro-organisms in the air, particularly in the operating room, has become more widespread, the questions most frequently asked have concerned the results obtained by its use and the possible danger to the patient and to the operating room personnel. Since probably I have had the greatest experience with this recent addition to surgical technic as a routine in all large clean operative procedures, a further report of my experience and results may be of interest and value in this field.

The first operation on a patient in the Duke Hospital in a field of ultraviolet radiation was performed on Jan 15, 1936. A preliminary report<sup>1</sup> based on several years' study of viable bacteria in the air, showing how they can be reduced by air conditioning and almost eliminated by radiation, was made after experience with 9 thoracoplasties had demonstrated great improvement in the local and systemic reaction of the patient. This was not published, however, until May 1937. Subsequently, in May 1936, a paper based on this preliminary work and on experience with 18 extrapleural thoracoplasties was read before the American Association for Thoracic Surgery and was published in October<sup>2</sup>. The operations on patients had been preceded by experimental studies on bacteria<sup>3</sup> and on wound healing in animals,<sup>4</sup> beginning

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From the Department of Surgery, Duke University School of Medicine and Hospital

1 Hart, D. Operation Room Infections. Control of Air-Borne Pathogenic Organisms, with Particular Reference to the Use of Special Bactericidal Radiant Energy, Preliminary Report, Arch Surg **34** 874-896 (May) 1937

2 Hart, D. Sterilization of the Air in the Operating Room by Special Bactericidal Radiant Energy, J Thoracic Surg **6** 45-81 (Oct) 1936

3 Hart, D., Devine, J. W., and Martin, D. W. Bactericidal and Fungicidal Effect of Ultraviolet Radiation. Use of a Special Unit for Sterilizing the Air in the Operating Room, Arch Surg **38** 806-815 (May) 1939

4 Hart, D., and Sanger, P. W. Effect on Wound Healing of Bactericidal Ultraviolet Radiation from a Special Unit. Experimental Study, Arch Surg **38** 797-805 (May) 1939

in the fall of 1934. The application of this technic to operations on patients was delayed, since it required approximately a year to interest a manufacturer in the project, and then the equipment had to be assembled and installed.<sup>5</sup>

From the opening of the Duke Hospital, in July 1930, until Jan 15, 1936, a total of 15,557 operations were performed, with 7 known deaths<sup>6</sup> resulting from infection in clean operative wounds (extra-pleural thoracoplasty, 4, craniotomy, 2, radical mastectomy, 1). From Jan 15, 1936 to Nov 1, 1939, all thoracoplasties, mastectomies and repairs of postoperative ventral hernias and most other large clean operations in the general surgical service have been performed in a field of ultraviolet radiation. For the past two and one-half to three years practically all large clean operative procedures in the neurosurgical, orthopedic and urologic services have also been performed in such a field. During these three years and nine and one-half months, of a total of 23,216 operations approximately 2,000 were clean operations performed in a field of bactericidal radiation. No patient operated on in this group, which includes most of the larger procedures, has died as a result of an operative wound infection.<sup>7</sup>

The results up to the fall of 1937, showing a reduction of over 75 per cent in all infections in clean operative incisions, have been reported. There were only two questionable operating room infections<sup>8</sup> (1) a stitch abscess and (2) a separation of the edges of the skin due to inversion of the skin, with a "positive" culture of material from the granulating area, in 364 clean primary incisions in the general and orthopedic surgical services when radiation was used. The infection rate for operations of an average magnitude less than that for these 364 operations was 3.5 per cent in 144 orthopedic and 3.6 per cent in 536 general surgical operations.

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5 The Westinghouse Electric and Manufacturing Company have supplied all radiation equipment.

6 There were probably other deaths from operating room infections in clean wounds in the other surgical services. A complete analysis is being made and will be published.

7 During this period 1 patient, on whom a craniotomy was performed without bactericidal radiation for an inoperable glioma when the only room equipped for radiation was in use for a laminectomy, died of meningitis (hemolytic *Staphylococcus aureus*). This was the only death during this period from an operating room infection in a clean incision in the general thoracic and neurologic surgical services. All the 23,216 records have not been reviewed and there may have been some deaths from operating room infections in other services in which radiation was not used. These are being reviewed, and the results will be published.

8 Hart, D. Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy. Results in Over Eight Hundred Operations. *Arch Surg*, **37**: 956-972 (Dec) 1938.

The considerable reduction in the average duration and elevation of postoperative temperature reaction for thoracoplasties, mastectomies and hemionrhaphies brought about by sterilization of the air has been reported.<sup>9</sup> These results were correlated with the seasonal fluctuations in the contamination of air, showing that the reduction in temperature reaction was directly proportional to the diminution in the degree of contamination of air.

TABLE 1—*Operations at the Duke Hospital from Nov 1, 1938 to Nov 1, 1939*

	Total	Postoperative Infections Diagnosed on Discharge of Patient		Postoperative Infections Found on Review of Records *	
		Number	Percentage	Number	Percentage
Total number of operations	6,535 <sup>a</sup>	23 <sup>b</sup>	0.35 <sup>c</sup>	Records not reviewed	
Clean primary incisions with bactericidal radiation	606	2 <sup>d</sup>	0.33	4 <sup>e</sup>	0.66
Total number of potentially infected or reopened wounds with bactericidal radiation	88	5 <sup>f</sup>	5.7	19 <sup>f</sup>	21.8

\* All these were related to the original disease or were either slight or questionable.

<sup>a</sup> All operations, including drainage of infected areas, operations on the nose and throat, transurethral prostatic resections, etc., are included.

<sup>b</sup> Under the rigid criteria which my associates and I use for healing without infection in the group in which radiation was used there were undoubtedly more than 23 infections, but the postoperative wound infections not diagnosed in the record have in general been slight or related to the preexisting disease. On previous occasions a careful analysis of records when radiation was not used has shown an infection rate of 3.5 per cent to 4 per cent for clean primary incisions exclusive of thoracoplasties.

<sup>c</sup> This percentage is low, since slight infections and infections related to the preexisting disease may not have been diagnosed, while the total number of operations includes the drainage of infections, operations on the nose and throat, transurethral prostatic resections, etc.

<sup>d</sup> One of these was an infection in an incision made through abraded skin and contused muscle for a fracture dislocation of the spine and was probably hematogenous (see abstract and temperature chart 3). The other was an infection following an arthroplasty of the hip, the wound was drained, and a postoperative hemorrhage occurred (see abstract and temperature chart 4).

<sup>e</sup> These infections (cases 1, 2, 5 and 6 [see abstracts and charts]) were slight, superficial, doubtful or due to a fault in technic. A brief abstract and postoperative temperature chart of each is given.

<sup>f</sup> See tables 3 and 4 for an analysis of these infections.

#### RESULTS OBTAINED

The first point of interest, the recent postoperative results obtained with bactericidal radiation, is illustrated by an analysis of the operations performed from Nov 1, 1938 to Nov 1, 1939. Table 1 shows that of a total of 6,535 operations bactericidal radiation was used throughout 606 clean primary incisions and 88 other operations in which the wounds were potentially infected or which involved reopening of a recent incision. Only 2 of the 606 clean primary incisions were diagnosed as showing postoperative wound infection at the time of the patient's dis-

<sup>9</sup> Hart, D., and Upchurch, S. E. Postoperative Temperature Reactions. Reductions Obtained by Sterilizing the Air with Bactericidal Radiant Energy. Seasonal Variations, *Ann Surg* **110** 291-306 (Aug) 1939.

charge One of the operations was a laminectomy in which I consider the infection to have been hematogenous even though the operation for a fracture of the spine of ten hours' duration was performed through abraded skin and contused muscles which were infiltrated with blood

TABLE 2—Operations Performed With Bactericidal Radiation from Nov 1, 1938 to Nov 1, 1939 (Clean Primary Incision)

Type of Operation	Without Postoperative Infection	With Postoperative Infection	Comment
Thyroidectomy, 63 laparotomy 23 thoracotomy, 2 miscellaneous, 67, lumbar incisions, 8	163	0	
Operations on breast radical 28 simple 9, excision of benign tumor 11	48 <sup>a</sup>	0	
Amputation, 8 operation for bone tumors 23 open reduction of fractures 17, spinal fusion, 11	59	0	
Operation for hernia inguinal, 80 femoral, 4 umbilical, 2 postoperative ventral, 10	90	1 <sup>b</sup>	Stitch abscess maximum temperature, 37.6 C
Craniotomy	90 <sup>c</sup>	1 <sup>d</sup>	Stitch abscess incision in scar spinal fluid drainage
Laminectomy (including meningocele repair)	57	1 <sup>e</sup>	Abrasion and contusion of skin infection (hematogenous ?)
Opening of joints	35	2	In 1 drainage and hemorrhage <sup>f</sup> ; In 1 necrosis of skin <sup>g</sup>
Extrapleural thoracoplasty	16 <sup>h</sup>	1 <sup>i</sup>	
Plastic procedures	37 <sup>j</sup>	0	
Total	600	6	

\* Diagnosed on the patient's discharge from the hospital. Other infections were slight questionable or related to the primary disease and were found on careful review of the records resulting from a poor blood supply due to close cutting of the skin flaps.

a Four of these were associated with some necrosis of the skin (without evident infection).

b See abstract and temperature chart 1.

c Two of these followed roentgen treatment and one without such treatment showed small areas of cutaneous necrosis while two of them had cerebrospinal fluid drainage. All however, were without evidence of infection.

d See abstract and temperature chart 2.

e See abstract and temperature chart 3.

f See abstract and temperature chart 4.

g See abstract and temperature chart 5.

h See abstract and temperature chart 7. In 1 of these cases in which there was a normal temperature after the third postoperative day organisms were cultured from a pocket of fluid in the wound (grossly not infected) at the time of the second operation.

i See abstract and temperature chart 6.

j After certain of these operations performed in multiple stages there may have been a "positive" culture of material from a granulating area where the skin could not be closed but none of the wounds showed suppuration or interference with the operative procedures.

(case 3) The other was an arthroplasty of the hip in which a drain was inserted and the patient had a postoperative hemorrhage. The infection was first noted on the ninth day following operation and was considered to be superficial, resulting from the open drainage tract and the hematoma in the wound (case 4). Four other infections, mostly slight or questionable, were picked up on careful review of the 606 records. The classification of these operations is given in table 2. In

order to present as complete and as accurate a picture as possible, every infection, however questionable, is included, even though I may feel that it occurred as a result of the technic used (case 5 and possibly case 4) or that the infection was not received in the operating room (stitch abscesses, cases 1 and 2). There are presented a brief abstract of each case record and the temperature chart for seven days after operation in each case of a clean incision which has been included as possibly infected. Each reader can then, make his own interpretation as to whether there was an infection originating in the operating room. The infection rate of 1 per cent, as shown in table 2, can therefore be lowered by individual interpretation of these abstracts but not raised.

Data on the reopened wounds are given in table 3. Of the 2 thoracoplasty incisions noted as infected, 1 had shown an infection following the

TABLE 3—*Operations Performed With Bactericidal Radiation from Nov 1, 1938 to Nov 1, 1939 (Reopened Wounds—Second Stage Operations)*

	Without Postoperative Infection	With Postoperative Infection
Extrapleural thoracoplasty	5	2 (1 with infection in first stage <sup>a</sup> 1 with organisms in wound <sup>b</sup> at operation)
Thyroidectomy (2d lobe)	10	0
Laminectomy	1	0
Postoperative ventral hernia	1 <sup>c</sup>	0
Total	17	2

a See abstract and temperature chart 6. This infection was diagnosed on discharge of the patient from the hospital. There was an undiagnosed infection (considered by the operator as only a draining hematoma) following the first operation, a granulating area was excised at the time of the second operation, and cultures of material taken from deep in the wound at this time showed viable hemolytic yellow staphylococci to be persistent.

b See abstract and temperature chart 7. The hemolytic *Staph aureus* was cultured from a pocket of fluid beneath the scapula at the time of the second operation. This infection with the same organism following the second operation was slight, the organisms being cultured from a draining hematoma, and the drainage never became purulent.

c. Infection was suspected the wound was explored in the operating room, no pus was found, cultures were sterile, the wound was reclosed without drainage, and primary healing resulted.

first stage, a granulating area was excised in making the incision for the second stage, and viable organisms were present deep in the wound. The other showed a positive growth of organisms from a pocket of fluid beneath the scapula at the second operation. Both infections were mild (See abstracts and temperature charts 6 and 7 for both first and second stages). These 2 infections in the reopened wounds were evidently continuations of the condition originating from entrance of the organisms at the time of the first operation. I still believe that viable organisms enter every wound, but with radiation these are greatly reduced and the survivors may be attenuated. The rate of infection in the thoracoplasty incisions is out of all proportion to the rate of infection in a



TABLE 4—Operations Performed With Bactericidal Radiation from Nov 1, 1938 to Nov 1, 1939 (Infected or Potentially Infected Incisions)

Type of Operation	Without Postoperative Infection	With Postoperative Infection	Comment
On colon 5 on stomach and Intestine 6 on appendix, 5, on gallbladder, 5	19 <sup>a</sup>	3 (1 colon*)	
Lobectomy and pneumonectomy	7 <sup>b</sup>	0	
Hernia Inguinal	0	1 <sup>c</sup> *	Local dermatitis
Femoral	0	1 <sup>d</sup>	Gangrenous Intestine
Pylephlebitis, drainage of splenic abscess	0	1 <sup>e</sup>	
Secondary closure	0	1 <sup>f</sup>	Infection around tension sutures
Excision of ulcer, skin graft	1	2	
Operations on kidney and on ureter	20	6 <sup>g</sup>	Drainage in all infected urine in all 4 very slight infections no severe infections
Meningocele repair (abscess opened during operation)	0	1	
Craniotomy (lacerated scalp—infected)	0	1	
Craniotomy (for subdural and extradural hemorrhage)	0	1 <sup>h</sup>	Followed wound rupture with sinus formation two preceding aspirations cultures sterile
Bone graft (for old osteomyelitis)	0	1 <sup>i</sup>	
Opening joints arthroplasty of hip in infection and abrasions of skin	0	1 <sup>j</sup>	
Removal of cartilage from knee infection of skin	0	1 <sup>j</sup>	Organisms cultured from joint at operation V B C, 10 200 per cu mm mild or doubtful
Old pyarthrosis of wrist scar, unable to close	0	1	
Total	47	27	

\* Diagnosed on the patient's discharge from the hospital. Other infections were slight questionable or related to the primary disease and found on review of the records

a In some of these cases there may have been a positive culture of material from the drainage tract but there was no gross suppuration and no drainage from other parts of the wound

b In 3 of these cases the wound was drained. Cultures showed no growth after operation but they yielded bacteria after a more or less prolonged period of drainage

c This operation should not have been performed since a note the day before operation described a dermatitis in the operative region

d Resection of gangrenous intestine

e Exploratory laparotomy. A splenic abscess secondary to pylephlebitis resulting from undiagnosed appendicitis was found and drained

f Only the reaction about cutting tension sutures of wire inserted for secondary closure of a disrupted laparotomy incision

g Most of these showed nothing more than slight infection when the drains had been left in for several days

h The hematoma reformed. It was aspirated twice and the cultures were sterile. A culture yielding bacteria was obtained only after rupture through the incision had occurred with formation of a draining sinus

i The patient was admitted from the dispensary with a note that admission was advised for the purpose of treating the cutaneous condition (furuncles and abrasions on the leg) on which the arthroplasty was to be performed. Two days later for some reason not explained, an arthroplasty was performed. Evidently this operation should have been postponed

j The patient showed furuncles on the leg and a leukocyte count of 10 200 per cubic millimeter before operation. The hemolytic Staph aureus was cultured from the fluid in the joint when it was opened. On the fourth day after the culture of material taken at operation was reported as yielding bacteria the wound was opened superficially and a note was made that it was infected but cultures of material taken at this time were sterile. On the ninth postoperative day the suprapatellar burr was irrigated and culture showed no growth. On the eleventh postoperative day material from the superficial tissues of the wound showed Bacillus alcaligenes faecalis. Twenty nine days later the wound was healed and the knee had the full range of motion

larger series of thoracoplasties previously reported as performed with the aid of radiation <sup>10</sup>

Table 4 records the potentially infected operative wounds and is of little significance here except as it illustrates some of the operations performed with bactericidal radiation and includes all operations with radiation not given in tables 2 and 3

Table 5 shows data on all other postoperative infections (operations performed without bactericidal radiation) diagnosed at the time of the patient's discharge It is seen that all these infections except those in the obstetric and gynecologic services were directly related to the primary disease There were undoubtedly other mild infections or infections related to the primary disease in the cases in which radiation was not

TABLE 5—Operations Performed Without Bactericidal Radiation from Nov 1, 1938 to Nov 1, 1939 (All Postoperative Infections Diagnosed on Discharge of Patient)

Operation for	Total Number of Postoperatively Infected Wounds *
Acute appendicitis	5
Acute cholecystitis	3
Intestinal obstruction	1
Perforated duodenal ulcer	1
Cesarean section	2
Hysterotomy, 1, hysterectomy, 1	2
Perineal laceration	2

\* Only infections diagnosed at the time of the patient's discharge The several thousand records of wounds not diagnosed as showing infection were not reviewed as was done for the operations performed with use of radiation

a Six of these were in the obstetric and gynecologic service, in which radiation is not used. The others were all related to the primary disease All large clean operations in the general, urologic, orthopedic and neurologic surgical services were performed in a field of bactericidal radiation, and data on them are shown in tables 2, 3 and 4 This table is included to show the types of operation in which radiation was not used as well as to report all diagnosed wound infections occurring when radiation was not used

used, but it can be safely assumed that there were no serious infections in clean wounds, since these are included in the diagnosis file Review of these several thousand records of operations performed without use of radiation for mild infections, such as stitch abscesses, did not seem indicated for this report This table is given to show all diagnosed post-operative infections occurring when radiation was not used and indicates that all large clean operations except those in the obstetric and gynecologic service were performed in a field of ultraviolet rays

SAFETY OF THE PATIENT

The second point of interest, the safety of the patient, is best proved by the fact that with an intensity of radiation on the wound varying

10 Hart, D Sterilization of the Air in the Operating Room with Bactericidal Radiation, J Thoracic Surg 7 525-535 (June) 1938

from 25 to 34 microwatts per square centimeter with different installations,<sup>11</sup> without any allowance for shading by the personnel, my associates and I have performed over 2,000 operations (general, thoracic, plastic, orthopedic, urologic and neurologic procedures), the majority lasting for from one to several hours, and have never seen any ill effects on, or had any complaint from, any patient referable to the radiation. Before this radiation was used on patients, many experiments were made on bacteria<sup>3</sup> to determine its killing effect, and many operations were performed on rats and on dogs<sup>4</sup> to determine the possibility of its damaging the tissues. During the earlier operations an assistant was assigned the duty of seeing that every part of the wound was covered when exposure was not absolutely necessary for the operative procedure. It was soon learned that this precaution was not necessary, so that now the tissues are covered with moist cloths or cotton, as determined by good surgical technic, but this duty is not assigned to an overzealous assistant instructed to protect them from the radiation even at the expense of the surgeon's efficiency.

Criticism of the intensity of radiation used by my associates and me was made in a recent article<sup>12</sup> stating that this is greater than is necessary to reduce the organisms in the air, that it may be in the danger zone for tissue injury and that there is an apparent inconsistency in the fact that we found that a blond subject suffered only mild erythema after eighty minutes' exposure, while they found that at the intensity which *they assumed* that we used an intense erythema was produced on the inner aspect of the arm of a blond human subject with an exposure of fifteen minutes.

These criticisms were made on *their assumption* that we were using 56.43 ("33 clicks  $\times$  1.71 microwatts per sq cm per click at 1 meter") microwatts per square centimeter on the wound. As a matter of record, we have stated in two publications<sup>11</sup> that the intensity of radiation used by us has been 28 to 30 microwatts per square centimeter at the operative site. When this reported figure (approximately 50 per cent of their assumed but false figure) is taken into consideration, their work (so far as it goes, being entirely experimental, performed on bacteria and animals without clinical application) is a corroboration of the efficiency and safety of the intensity of radiation which we have used and advocated.

11 Hart and others<sup>3</sup> Hart and Sanger<sup>4</sup>

12 Kraissl, C. J., Cimiotti, J. G., and Meleney, F. L. Considerations in the Use of Ultraviolet Radiation in Operating Rooms, *Ann Surg* **111** 161-185 (Feb) 1940

Our early work was done without the advantage of a meter for recording the intensity distribution of the radiation, so that exact measurements could not be given in our early publications. During the past three and one-half years, however, first with an assortment of equipment which was mounted on a supply truck and later with the compact meter which has since been developed by Westinghouse for simplification of the measurement of this radiation, the output of all radiation units, including the original experimental installation, has been checked regularly. The intensity distribution of each radiation unit as measured by a photoelectric cell sensitive to its predominant wavelength (over 88 per cent of the output at 2,537 angstrom units) and calibrated with a bismuth silver vacuum thermopile has been correlated with the distribution of bacteria as determined by the sedimentation method.

A number of different arrangements of ultraviolet radiation units have been tried, the results on four of which were demonstrated in a scientific exhibit at the meeting of the American Medical Association in Atlantic City, N. J., in June 1937 and have been on continuous exhibit in the Duke Hospital operating suite since that time. Only one of these gave more than 34 microwatts per square centimeter at the operative site,<sup>13</sup> and use of this was discontinued after a few trials because of the difficulty in protecting the personnel. There was, however, with this higher intensity no evident injury to any patient. The unit which we have used most during the past three years and which we are using exclusively, except for one of the new units developed by Westinghouse which we have recently installed, gives an intensity of 25 microwatts per square centimeter at the operative site, with a reduced intensity on the heads of the operating team and a higher intensity in all other parts of the room (floor, periphery and upper air) as compared with the other installations which we have tried. This unit, which delivers the least radiation on the wound, has been the most effective in reducing the number of viable sedimenting bacteria in every part of the operating room, including the operative site. These data, illustrating the desirability of effectively irradiating the entire room, were given to Westinghouse for the development of the unit which they have recently made available. Publication of the intensity distributions and bactericidal effect of these various installations has been withheld in order to include studies on this new unit. These data will be published at an early date.

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13 All the intensities given are the actual measurements without any obstruction to the rays. During use in an operation it is estimated that from 15 to 25 per cent or more of the radiation is kept from the region of the wound by shading. Air tissue not on a flat exposed surface would receive less than half of the intensities given by measurements made without any obstruction.

## SAFETY OF PERSONNEL

In regard to the danger to the operating room personnel, there are two risks to be considered, those due to acute exposures and those following often repeated slight or more prolonged exposures over a long period. Irritation of the skin from either type of exposure can be avoided easily by adequate covering or shading. The eyes can apparently be adequately protected by glasses and a close-fitting eye shade or hat, or, if one desires to be certain that no ray reaches the eyes, goggles can be worn. I have never seen a blister form on a patient or a member of the staff, and many of the nurses, anesthetists and orderlies do not cover their arms, necks or faces, wearing only glasses and a sun helmet in addition to the usual cap and mask. A few persons wearing no protection whatever have had conjunctivitis of sufficient severity to require local anesthesia, but this has always cleared within one or two days, without evident sequelae.

The possibility of chronic changes in the skin due to long-continued repeated exposures cannot be foretold. Experimental workers who have been exposed frequently for years report no ill effect. No harmful effect has been noticed on any of our staff. For the sake of safety, however, since the skin and eyes can be so easily shaded, every one using ultraviolet radiation should avoid unnecessary exposure until the risk of often repeated exposures over a long period is known. The rays have little power of penetration, closely woven starched cloth being sufficient to stop over 99 per cent of them, so that protection is relatively easy.

In order to simplify the protection of the personnel, certain of the radiation tubes in the units which we are now using have been placed at a higher level (10 feet 6 inches [above the floor]). Their output has been increased so as to give a slightly diminished intensity on the wound, a greatly diminished intensity on the heads of the personnel, a higher intensity at the floor and at the periphery of the room and a much higher intensity in the upper parts of the room, where the bacteria are carried by the convection currents. Not only does the additional height of these units as compared with the lower ones give a lower intensity on the heads of the personnel, but the ray which strikes them comes from a more nearly vertical direction, thus simplifying the problem of shading the eyes, the bridge of the nose and the adjacent skin.

## SUMMARY

In approximately 2,000 clean incisions for operations of greater magnitude in the general, thoracic, urologic, orthopedic and neurologic surgical services performed in a field of bactericidal radiation no patient has died as a result of an infection in the wound.

During the past year bactericidal radiation was used for 606 such clean primary incisions in a total of 6,535 operations of all types, with an infection rate of less than 1 per cent. Several of these infections probably were not received in the operating room, and not one was severe.

The few infections reported have been mild or questionable, and the total has been 1 per cent or less for all operating room infections in clean primary incisions. Exclusive of thoracoplasties, and if stitch abscesses and separations of the skin with a superficial granulating area are not considered as operating room infections, the infection rate for all operations reported by my associates and me<sup>14</sup> has been less than one third of 1 per cent (cases 3, 4 and 6 in this report).

The intensity of radiation (over 88 per cent output at 2,537 angstrom units) used is much less than 30 microwatts per square centimeter when shading is taken into consideration, and for most of the recent operations the intensity at the operative site has been only 25 microwatts per square centimeter, without allowance for shading.

In a recent article on ultraviolet radiation in the operating room<sup>15</sup> our work was criticized on the false assumption that we used a radiation intensity of 56.43 microwatts per square centimeter instead of approximately one-half that intensity, as we had previously stated<sup>11</sup>. With this false assumption corrected to our published figure the criticisms are not valid, and the work, so far as it goes, confirms the effectiveness as well as the safety of the intensities of radiation which we have used and advocated.

Animal experiments previously published<sup>4</sup> indicate that the intensities which we have used will not damage the tissues of the wound during the time they would be exposed during any operation if precautions are taken to prevent drying and unnecessary exposure of the tissues to the air.

No patient has ever made any complaint referable to, or received any evident injury from, the radiation.

The personnel can be adequately protected without loss of efficiency, and they should not take the risk of frequent or prolonged unnecessary exposures. Despite instructions otherwise, our personnel have taken many liberties with the skin, without evident damage other than an occasional mild and transient erythema. Many of the nurses and anesthetists do not cover the customarily exposed cutaneous surfaces except for the usual cap and mask supplemented by a hat and glasses.

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<sup>14</sup> All operations performed with bactericidal radiation have been reported with the exception of a consecutive block from the fall of 1937 to Nov 1, 1938. This group has not been reported on, and so the records have not been reread in a search for slight infections which may not have been entered on the diagnosis when the patient was discharged.

The eyes *must* be protected by glasses, and a closely fitting eyeshade or hat. In a few cases of conjunctivitis brought on by neglect of this precaution local anesthesia has been required, but this condition has cleared within one to two days, without evident sequelae.

#### ABSTRACT OF CASES

CASE 1—Bilateral indirect inguinal hernias of two years' duration in B W, a 47 year old white man, were repaired with the patient under cyclopropane anesthesia, a silk technic being used. The Wassermann reaction was 4 plus, and the Kahn reaction, 1 plus. The virtual absence of elevation of temperature after operation is shown in chart 1. During the remainder of his stay in the hospital, no temperature higher than 37.3 C (99.1 F) was recorded. On the sixth post-operative day, when the sutures were removed, there was reddening about some of them, with small stitch abscesses. Three days later all evidence of the infection had disappeared, and convalescence was entirely uneventful. This is a case of reaction of the tissues to a foreign body with growth of cutaneous organisms about the sutures and not one of "operating room infection."

CASE 2—A cerebellar approach through the old scar was made for a recurrent astrocytoma in J N, an 18 year old white boy. Leakage of spinal fluid occurred

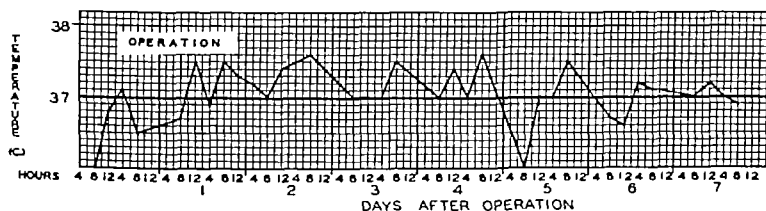


Chart 1—Record of temperature in case 1

on the fourth day following operation, and on the sixth day a stitch abscess was found at the right end of the incision. At this time leakage of spinal fluid had ceased spontaneously. On the eleventh postoperative day fluid aspirated from the wound contained 900 cells, and culture revealed *Staphylococcus albus* and a gram-negative bacillus. The patient was treated with sulfapyridine. On the seventeenth day following operation the wound again began to drain. The sinus tract was excised and closed, three galeal and three skin sutures of silk being used. The temperature curve for seven days after the major operation is shown in chart 2. During the subsequent course there were two short periods of elevation of temperature, one at the time of the wound aspiration and the other following rupture and secondary closure of the wound on the seventeenth postoperative day. Convalescence otherwise was uneventful, and the patient was discharged twenty-nine days after operation.

CASE 3—A laminectomy was performed in J M, a 25 year old Negro ten hours after injury, through abraded skin, contused muscle and extravasated blood for a fracture dislocation of the first lumbar vertebra. The temperature curve for eight days after operation is shown in chart 3. The rise on the fifth and sixth days was caused by pneumonia, diagnosed by physical signs and confirmed by roentgen examination, and the organisms were identified by culture of the sputum as hemolytic yellow staphylococci. The patient was treated with sulfapyridine.

On the sixth day without his having been catheterized, a few white blood cells were first noted in the urine. On the seventh the wound, which was not tender, was probed, but no pus was found. On the ninth, the hemolytic *Staph. aureus* was cultured in material from the wound.

On the eleventh day the urine was described as grossly infected, and the hemolytic *Staph. aureus* was grown on culture, and an indwelling catheter was inserted. On this day a blood culture showed 1 colony of the hemolytic *Staph. aureus* per cubic centimeter.

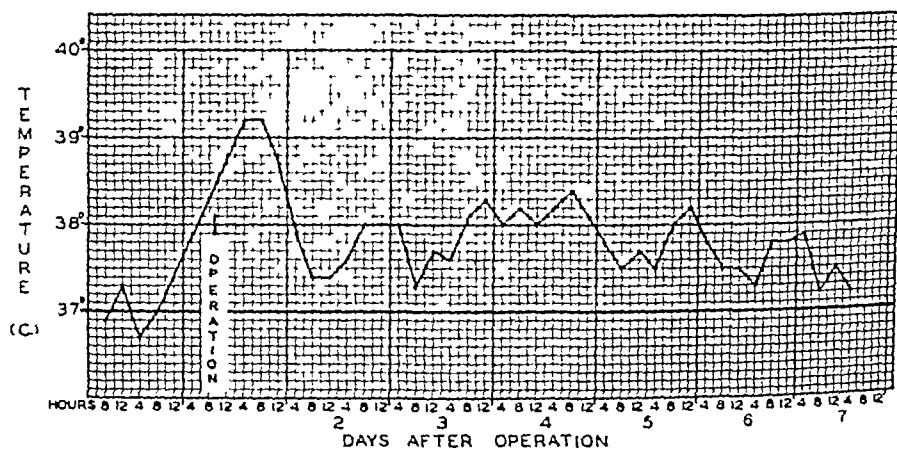


Chart 2—Record of temperature in case 2

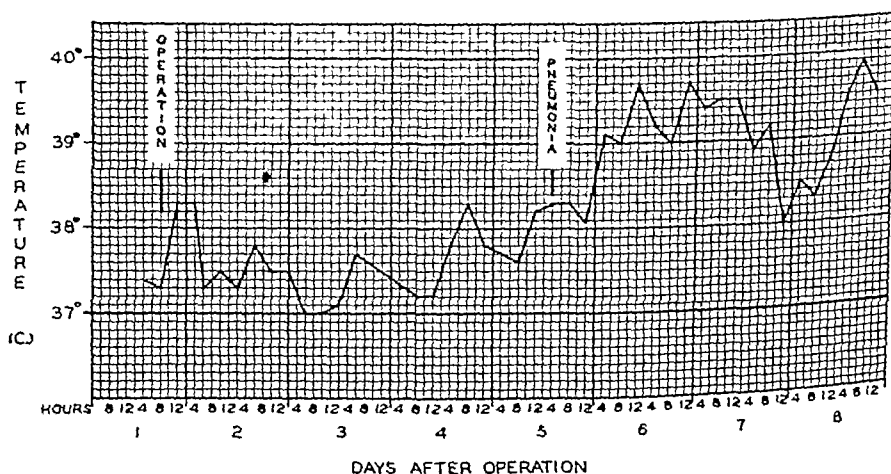


Chart 3—Record of temperature in case 3

The irregular temperature, reaching its peak on the eighth postoperative day, fell rapidly and from the twelfth to the thirty-eighth day was in general below 38°C, (100.4°F) with irregular peaks somewhat above this. After the thirty-eighth day it remained below 38°C. The wound infection did not extend to the spinal canal, and the process in the chest cleared slowly, but the persistent moderate elevation of temperature was probably due to the infection of the urinary tract in a paralyzed patient.<sup>15</sup>

15 I consider that this wound infection was hematogenous and secondary to the pneumonia. During this twelve month period there were 2 other infections following operation (cesarean section and appendectomy) performed with-

(Footnote continued on next page)



CASE 4—W L, a 27 year old white man with an ankylosis of the left hip underwent an arthroplasty with insertion of a vitallium cup. A drain was inserted, and after operation there was a severe hemorrhage from the wound. The temperature curve for seven days after operation is given in chart 4. The drain was removed on the third postoperative day. On the ninth postoperative day the dressings were removed, and some superficial infection was present, cultures showing the hemolytic *Staph aureus*. This is thought to have resulted from the hematoma in the wound with the persistent drainage tract. There was a rise of temperature to 39.5 C (103.1 F) on the ninth and tenth days, but the temperature dropped to normal by the twelfth day and remained below 37.5 C (99.5 F) for the next four and one-half weeks, or two weeks after motion and physical therapy were started. There was a slight rise in temperature then, but during the next twenty weeks there were only twelve recorded temperatures (temperature taken every four hours) above 37.5 C and only one above 38 C. The cup was then removed. There was some granulation tissue about the cup but no destruction of bone. After this the patient's condition remained good, and nine weeks after removal of the cup he had 25 degrees of flexion, 15 degrees of extension, 15 degrees of adduction and 25 degrees of abduction.

bactericidal radiation, and these infections were considered by me to have been hematogenous and secondary to pneumonia. A brief resume of these cases follows.

An appendectomy for acute appendicitis (appendix unruptured) was performed on Sept 4, 1939. On the second postoperative day there was bilateral bronchopneumonia. Sputum for culture could not be obtained. On the sixth day the incision was well healed, with no infection. On the seventh day there was pericarditis, with fluid in the right side of the chest. On the sixteenth day the incision was well healed. On the twenty-fourth day there was an abscess in the neck. On the twenty-fifth day an abscess developed at each venipuncture wound. There were abscesses also on the back, arms and neck. On the thirty-fifth day there was an abscess in the abdominal wall, involving the incision. On the forty-second day the temperature was normal and remained down for the remainder of the course in the hospital. On the sixty-seventh day the patient was discharged, recovered.

The patient was treated with sulfapyridine to the seventeenth postoperative day. The leukocyte count dropped to 1,950 per cubic millimeter by the twenty-third day. Staphylococcus antitoxin, 300,000 units, was given between the twenty-fifth and the twenty-eighth postoperative day. On the twenty-eighth day the leukocyte count was 12,850 per cubic millimeter, and by the thirty-second it was up to 20,800. All blood cultures were sterile. The urine did not become infected, and no sputum could be obtained for culture. All other cultures showed a pure growth of the hemolytic *Staph aureus*. The temperature remained normal after the forty-second postoperative day.

A cesarean section was performed without bactericidal radiation on Nov 1 1938.

On the third day following operation the patient had pneumonia. The hemolytic *Staph aureus* was grown on culture of the sputum.

On the tenth day the urine was infected with the *Staph aureus* (hemolysis not noted).

The first evidence of wound infection was noted on the sixteenth day. Cultures showed the hemolytic *Staph aureus*.

The patient recovered.

At the time of writing there is still a small sinus with a slight amount of discharge. The temperature was elevated for three days after the removal of the cup, and since that time has remained practically normal.

**CASE 5**—Open reduction of a fracture dislocation of the ankle of three and one-half months' duration, with lengthening of the tendon of Achilles, was performed in L. E., a 43 year old Negro who had a psychosis during the postoperative course. Six days after operation he had conjunctivitis (hemolytic *Staph. aureus*). The cast was removed on the thirteenth postoperative day, and the skin, which had been closed with catgut, was found to be separated, with some superficial but no deep-seated infection (Cultures were not made). The temperature, which was as high as 37.7 C (99.8 F) before operation, is shown for seven days after operation in chart 5. During the next twenty days the temperature reached 38.1 C.

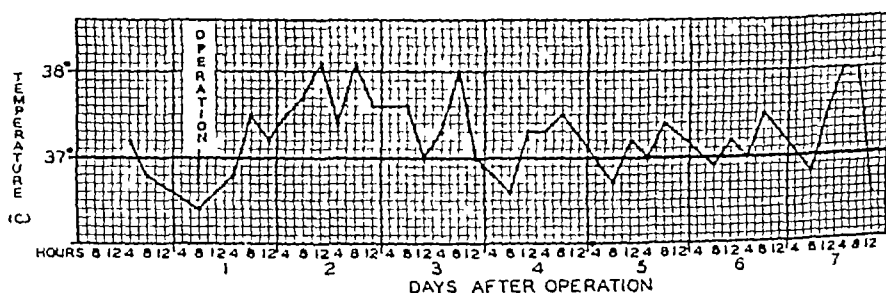


Chart 4—Record of temperature in case 4

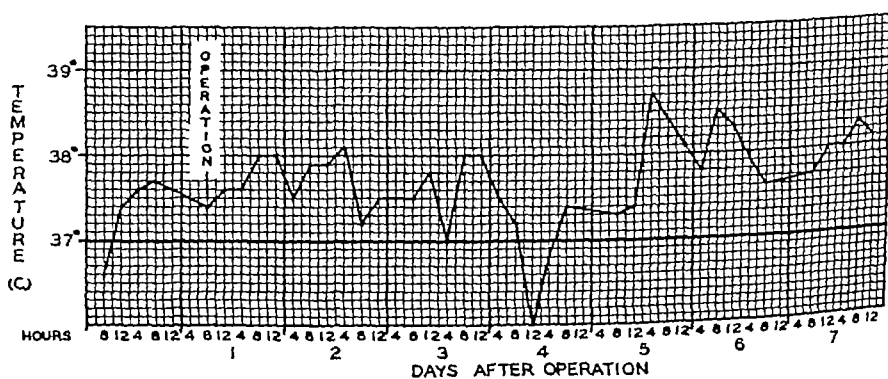


Chart 5—Record of temperature in case 5

(100.5 F) on three, 38.2 C (100.7 F) on three and 38.4 C (101.1 F) on two occasions, otherwise it remained at or below 38 C. Only the superficial part of the wound exposed by the separation of the skin was infected, and the patient was known to harbor the hemolytic *Staph. aureus* (conjunctivitis).

**CASE 6**—A. A., a 26 year old Negress with tuberculosis of the right lung of fourteen months' duration underwent resection of the three upper ribs with apicolysis. During the freeing of the apex an enlarged lymph node was encountered and removed.

On the ninth postoperative day the wound was probed, and what was apparently a liquefied hematoma was evacuated. Cultures showed *Staph. aureus* and *Staph. albus*. In the next note (two days later) and in all subsequent notes the wound was described as clean and dry without drainage on the dressings. The temperature curve is shown for seven days in chart 6, first stage. There was a very gradual fall in temperature to the twenty-fifth postoperative day, after which the readings remained below 37.5 C. (99.5 F).

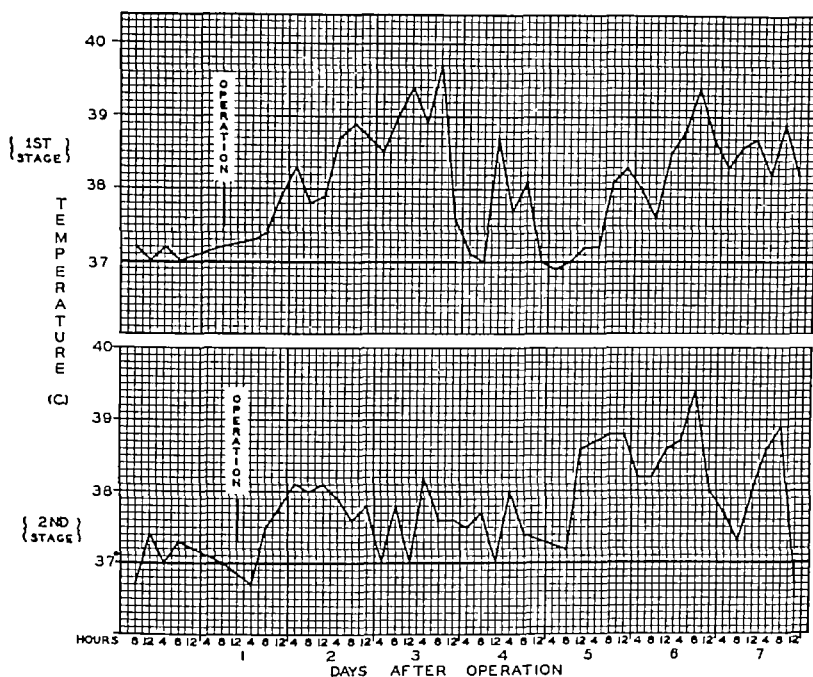


Chart 6—Record of temperature in case 6

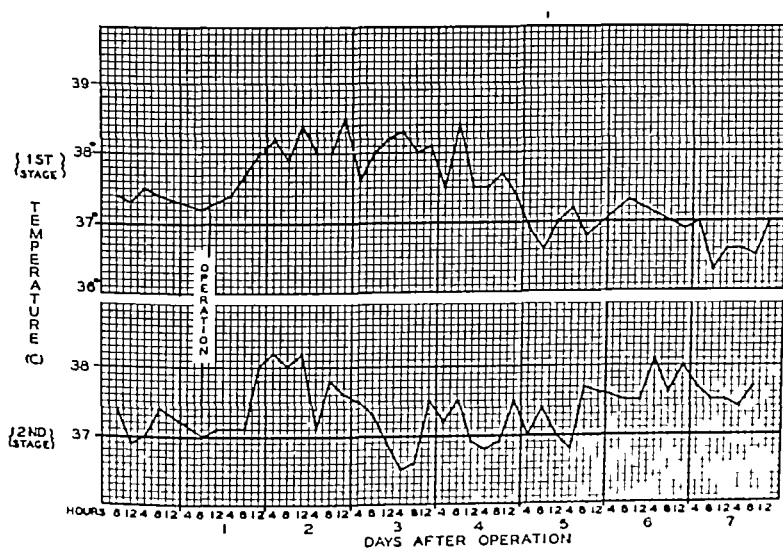


Chart 7—Record of temperature in case 7

The second operation, resection of parts of the fourth through the seventh ribs, was performed thirty-one days after the first stage. The operative note reports the excision of an ulcer in the old scar, although the preceding notes had reported that the wound was dry and that there was no drainage. There was no evidence of infection at the second operation, but cultures of material from the depths of the wound showed the hemolytic *Staph aureus*. The temperature curve for the first seven days following operation is shown in chart 6 (second stage). The temperature remained below 38 C after the eighth day. On the seventh post-operative day, 100 cc of bloody fluid was evacuated from a hematoma in the incision, and on the ninth day cultures showed the hemolytic *Staph aureus*. Bloody drainage continued to the twentieth day, and on the twenty-sixth day all drainage had stopped. On the thirtieth day after operation there was only a superficial unhealed area 3 mm long.

In the first stage the wound was not considered by the operator to be infected, the elevation of temperature being explained as due to pulmonary spread, but the subsequent culture reports make the diagnosis of infection conclusive even though it may not have been responsible for the elevation of temperature. The reason for performing the second operation when an ulcerated area had to be excised in making the cutaneous incision for the second stage was not given. The second stage operation should have been postponed. The field was evidently infected by viable organisms persisting in the wound from the infection in the first stage.

CASE 7—C B, a 42 year old white woman with tuberculosis of the right lung of four years' duration, underwent resection of the upper three ribs with apicolysis. The postoperative course was uneventful, the wound healing without evidence of infection. The temperature curve for seven days after operation is shown in chart 7 (first stage), and from this time until the next operation the temperature remained below 37.5 C.

The second stage, with resection of parts of the fourth through the sixth ribs, was performed fourteen days after the first stage. There was a large pocket of fluid in the defect left by the apicolysis. On gross inspection this was apparently uninfected, but cultures revealed the hemolytic *Staph aureus*. When the sutures for the second stage were removed on the seventh day there was an escape of "20 to 30 cc of dark blood and fat droplets." Cultures showed the hemolytic *Staph aureus*. Drainage of chocolate-colored material continued to the thirteenth day, and on the twenty-sixth day all drainage had ceased. The temperature curve for the first seven days after operation is shown in chart 7 (second stage). During the subsequent course in the hospital (thirty-seven days after operation) the temperature did not go above 37.6 C (99.6 F).

# CONTRIBUTION OF THREE EARLY BRITISH SURGEONS TO KNOWLEDGE OF HEART DISEASE

JAMES B HERRICK, M D

CHICAGO

The primary motive that has induced me, an internist, to accept the kind invitation to have a share in this special number of the ARCHIVES OF SURGERY is that by so doing I may show my appreciation of, and affection for, Dean Lewis. To have known him as a student, intern, faculty and hospital colleague and congenial companion is to have an abiding sense of his superior ability as a surgeon, teacher and medical leader, and of his genius for making and holding friends.

I trust it may not seem inappropriate to reiterate in this paper the truth that medicine and surgery are, and should be, closely related and mutually helpful, and, as a concrete illustration of the debt owed by medicine to surgery, to call attention to the worth while contributions made to the knowledge of heart disease, a little more than a century ago, by three British surgeons.

At that time, in the early eighteen hundreds, when nothing was known of bacteriology, anesthesia or x-rays, when at the bedside practically no use was made of the microscope or of chemistry, when there was no auscultation or application of electricity in diagnosis or treatment, the well educated medical man possessed and utilized a much larger proportion of the existing medical knowledge than is possible today. Dividing lines between different types of practitioners were not so sharply drawn as they are at present. There were really but two outstanding specialists—the physician—the internist—and the surgeon, though many were known as obstetricians and the ophthalmologist and the dermatologist were bidding for recognition. As a matter of fact the surgeon was but the physician who was distinguished by his more accurate knowledge of anatomy and his dexterity as an operator. At the bedside and at the necropsy table, as well as at operations, the surgeon made observations that had a bearing that was general and not limited to his own specialty. As an example may be named John Hunter. That the process was a reciprocal one is shown by the work of such an internist as Edward Jenner. Happily, this mutual interchange of knowledge is still going on between medical specialists of every type and between medicine and cognate sciences like chemistry, physics and

biology It is one of the chief agencies that are tending to make medicine more nearly an exact science

The three British surgeons were Joseph Hodgson of England, Allan Burns of Scotland and Robert Adams of Ireland<sup>1</sup> While their contributions are of minor grade, they are yet of value It is remarkable that the authors were relatively young at the time they wrote Hodgson in 1815 was 27, Burns in 1809 was 28, Adams, writing in 1827, was older, though only 35

Allan Burns, son of the Rev John Burns, was born in Glasgow, Scotland, on Sept 18, 1781 He was precocious At 14 he began to study medicine At "sixteen he took upon himself the sole direction of the dissecting rooms of his elder brother, John Burns, who at that time was an extramural lecturer on Anatomy and Surgery at Glasgow" and who was later the author of a popular work on obstetrics Allan "soon made for himself a reputation as a practical anatomist" Unlike his brother John, he did not excel as a lecturer, but as a demonstrator and dissector he was *facile princeps*, with an enthusiastic following of students He studied disease also, both in the wards of the infirmary and in the morgue Not having a university degree, he had to obtain his experience as physician and surgeon chiefly by attending and studying the patients of his brother and of his friends He had no practice of his own In his case books he made notes and drawings that stood him in good stead when later he wrote on the diseases of the heart, on the blood vessels, on surgical anatomy and on hernia After an illness that one recognizes today as a recurring appendicitis, he died on June 22, 1813, when he was 31 years and 9 months old His death, terminating a brief but brilliant career, was, in the words of Duncan, "a severe blow to the Glasgow Medical School on which he had already shed lustre"

The first of the major works of Allan Burns was his "Observations on Some of the Most Frequent and Important Diseases of the Heart, on Aneurism of the Thoracic Aorta, on Preternatural Pulsation in the Epigastric Region, and on the Unusual Origin and Distribution of Some of the Large Arteries of the Human Body Illustrated by Cases" This was published in Edinburgh in 1809 In 1811 appeared his "Observations on the Surgical Anatomy of the Head and Neck Illustrated by Cases and Engravings" In addition to these books he contributed to medical journals several articles, chiefly surgical, that need not be mentioned here

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1 In writing this paper I quote freely from articles on Allan Burns (Herrick, J B Allan Burns 1781-1813, Anatomist, Surgeon and Cardiologist, *Bull Soc. M. Hist. Chicago* 4 457-483 [Jan] 1935, Robert Adams, Surgeon, and His Contributions to Cardiology, *Ann M. Hist.* 1 45-49 [Jan] 1939) that are already in print

A few of the more outstanding features of Burns's book on heart disease will be noted. He gave accurate anatomic descriptions of congenital anomalies and showed an intelligent understanding of the resulting disturbances. He discussed pericarditis in a fairly satisfactory manner. His anatomic diagnosis was clearcut. He described what is today called pericarditic mediastinitis when he referred to complete "matting" of the pericardium with the neighboring parts. He explained some of the signs, such as a "diffused undulation" rather than a decided pulsation, on the basis of adhesions to the diaphragm and other structures. He was explicit in emphasizing the reference of pain to parts other than the pericardium, such as the epigastrium or the shoulder. Again "Where also no change takes place in the spot where the pulsation is felt in the chest, when the patient turns from side to side we are assisted in our diagnosis" of adhesive pericarditis. Had Burns known of auscultation, percussion, bacteria, of albuminuria as evidence of renal disease, and of the importance of clinical thermometry, his description of pericarditis would have been equal to any written today.

In reading Burns, one is impressed by the broadness of his views, such as his conception of the unity of the heart and blood vessels, the modern notion of the cardiovascular system. He was anatomist, physiologist and pathologist as well as internist and surgeon. "Until," he said, "we possess clear notions respecting the natural functions of a part, our ideas concerning its morbid actions, can never be otherwise than vague and unsatisfactory. But often our opinions regarding healthy function are corrected by observing what takes place in disease."

Chapter 7, on disease of the coronary arteries and on syncope anginosa, is of special interest to cardiologists, for it contains Burns's statement concerning the myocardial ischemic theory of angina pectoris. With characteristic frankness Burns acknowledged his indebtedness to others and his unqualified adherence to the coronary artery theory of angina pectoris. "To Drs. Heberden, Jenner and Parry, we owe most of our information respecting this most fatal complaint," a condition which Parry "has incontrovertibly proved to originate from some organic laesion of the nutrient vessels of the heart."

He compared the heart with obstructed coronary vessels to a limb with a ligature. The limb can continue in vigorous action for only a short time, then weakness enforces rest. The heart "is principally composed of muscle and we have therefore reason to believe that it is regulated by the same laws which govern other muscles" (p. 143). The heart, like every other part of the body

has peculiar vessels set apart for its nourishment. In health, when we excite the muscular system to more energetic action than usual, we increase the circulation in every part, so that to support this increased action, the heart

and every other part has its power augmented. If, however, we call into vigorous action, a limb, round which, we have with a moderate degree of tightness, applied a ligature, we find that then the member can only support its action for a very short time, for now its supply of energy and its expenditure, do not balance each other, consequently, it soon, from a deficiency of nervous influence and arterial blood, fails and sinks into a state of quiescence. A heart, the coronary vessels of which are cartilaginous or ossified, is in nearly a similar condition, it can, like the limb be girt with a moderately tight ligature, discharge its functions so long as its action is moderate and equal. Increase however the action of the whole body, and along with the rest, that of the heart, and you will soon see exemplified, the truth of what has been said, with this difference, that as there is no interruption to the action of the cardiac nerves, the heart will be able to hold out a little longer than the limb (P 138)

If a person walks fast, ascends a steep, or mounts a pair of stairs, the circulation in a state of health is hurried, and the heart is felt beating more frequently against the ribs than usual. It, however, a person with the nutrient arteries of the heart diseased in such a way as to impede the progress of the blood along them, attempt to do the same, he finds, that the heart is sooner fatigued than the other parts are, which remain healthy. When, therefore, the coronary arteries are ossified, every agent capable of increasing the action of the heart, such as exercise, passion and ardent spirits, must be a source of danger (P 139)

Burns deserves credit as an early advocate of Parry's<sup>2</sup> theory of a lesion of the coronary artery and relative myocardial ischemia in angina pectoris and for having made a crude experiment to substantiate his theory.

For a discussion and explanation of the fact that Burns in his description of his experiment and in his application of the results of this test to conditions in the human heart stressed weakness and syncope rather than pain as the major cause compelling cessation of muscular action in the limb or heart, as well as for the comments of MacMillan and Webster (1923) and Sir Thomas Lewis (1932) on this feature of Burns's experiment, I refer the reader to pages 14 and 16 of my article on Allan Burns.<sup>1</sup>

In reading chapter 8, called "Observations on the Effects Resulting from Change of Structure of the Valves of the Heart and Large Arteries," one is impressed by the modernness of Burns's views. One sees also that he was more than a mere morphologic anatomist, that he was a pathologist who aimed to correlate judiciously the clinical and the pathologic findings. "We are not," he said, "in every case, where after death we find these appendages—the valves—opaque, to conclude that this change from the healthy transparent state, shall have been accompanied with a correspondent alteration in the function" (p 163).

He described a case of what today would be recognized as mitral stenosis with auricular fibrillation and congestive heart failure. The

<sup>2</sup> Parry, C. H. An Inquiry into the Symptoms and Causes of the Stricture of the Arteries, Commonly Called the Angina Pectoris, London, Cadell & Davis, 1772.



presystolic thrill, the sharp systolic impulse, the pulse deficit are all there as evidence of his accurate clinical observation. What is lacking is auscultation. The autopsy revealed the constricted indurated valve.

One of the best chapters is the ninth, on the formation of polypi in the heart. He made a clear distinction between antemortem and post-mortem clots, calling attention to differences in consistency, color, attachment to the wall of the heart and the like.

Burns discussed in a scholarly and scientific manner aneurysm of the thoracic aorta. This chapter reveals an extensive search of the literature, a careful survey of his own cases and a clarity, directness and conciseness in style that show more revision than is apparent in some of his other chapters. He considered pathogenesis, in general agreeing with Scarpa. He had experimented with rupture by injecting wax into the artery. The symptoms, which were fully discussed, were always interpreted in terms of anatomy. Unequal pulses, dysphagia and swelling of veins were considered not merely curious or mysterious phenomena, for "there must be some physical reason for this diversity of effect" (p. 243).

The substance of the chapter on the causes of preternatural pulsation in the epigastrium may be learned from the summary at the end of the chapter. "*Pulsation in epigastrio* may be produced by adhesions of the heart to the pericardium, by enlargement of the heart itself, chiefly of the right side, by tumours attached to the diaphragm, by enlargement of the vena cava inferior, by preternatural solidity of the lungs, by any solid increase of substance about the aorta, or roots of the large abdominal arteries, and lastly by a peculiar affection of the vascular system itself" (p. 276). In the latter condition, to judge from the histories presented, may have been included cases of exophthalmic goiter, severe anemia and, possibly, neurasthenia. There was a recognition of the so-called positive hepatic pulse.

His concluding chapter, of forty pages, was headed "Remarks on the Unusual Origin and Course of Some of the Large and Important Arteries of the Human Body" and was based on the observations and records made by Burns during his many dissections of the preceding several years. "All the descriptions, with the exception of a single one on the authority of my friend, Dr. Barclay, are taken from dissections made by myself or from preparations in my possession" (p. 322). Perhaps Granville Pattison did not exaggerate when he said that Burns's collection of vascular preparations was at one time, superior to any other in the world.

In 1811, when he was 30 years old, Burns published his observations on the "Surgical Anatomy of the Head and Neck, Illustrated by Cases and Engravings." Its style was less discursive than that of the volume on the heart. The volume is packed with suggestions on practical sur-

gery, it might be spoken of as a work on anatomic surgery rather than surgical anatomy. A great variety of topics with illustrative cases was taken up: esophagotomy, resection of the trigeminal nerve for tic douloureux, ligation of thyroid arteries for bronchocele, melanotic tumor of the eye with metastasis to the liver, etc. The work was highly regarded by Burns's surgical contemporaries and his immediate successors. Valentine Mott referred to the author as "this celebrated anatomist." Complimentary references were made by Abernethy and Sir Astley Cooper. Meckel, in a foreword to the Halle translation of 1821, spoke of it as not merely a compilation of known facts but a work that enriched the science and art of medicine through original observations and investigations. Duncan, in 1896, said "His work on the *Anatomy of the Head and Neck* is one of the most noteworthy contributions to anatomy which the Glasgow School has yet made." A second edition was published in Glasgow in 1824 and in Edinburgh in 1833. An American edition appeared in 1823.

The work of Burns cannot be regarded as epoch making, as was that of Laennec, for example, or that of Jenner. Yet his writings contain many evidences of such keen insight into facts and causes that one is tempted to speak of them as prophetic. Some were genuine contributions to knowledge, not always entirely new, but presented from a new point of view or with some illuminating addition. The coronary artery theory of angina pectoris and his experiment with the ligature, his clear statement of the back pressure theory of dilatation and hypertrophy whether from valvular obstruction or leakage and his discussion of antemortem thrombi and aortic aneurysm were notable contributions. He had the spirit of investigation—witness his careful records and specimens of arterial anomalies, his work on epigastric pulsation, his injection of arteries to show collateral circulation, his thorough postmortem examinations and his correlation of clinical and pathologic observations.

His treatise on heart disease, with all its faults, was pioneer. His book on surgery of the neck was an advance over anything previously published. He was progressive and capable of growth. Had he lived to know of Laennec and Louis, of Skoda and Rokitansky, he would, whether practicing and studying as a surgeon or as an internist, have been one of the leaders among the choice group of British clinicians, whose names add brilliancy to the first half of the nineteenth century, a group containing, among others, such men as Stokes, Bright, Addison, Graves, Astley Cooper and Paget.

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In 1811 Joseph Hodgson (1788-1869), then a young man of 23, "—awarded the Jacksonian prize of the College of Surgeons of London—his essay on "Wounds and Diseases of the Arteries and Veins" "

supplementary paper with illustrative cases was presented in the same year. These two contributions, so he said, were the basis of his work published in 1815, "A Treatise on the Diseases of Arteries and Veins, Containing the Pathology and Treatment of Aneurysms and Wounded Arteries" <sup>3</sup>

Hodgson, a surgeon, naturally considered aneurysm, varicose veins and wounds of blood vessels chiefly from the surgical point of view. The symptoms, signs and diagnosis, together with the dangers and natural history of untreated conditions and the various plans of treatment, were minutely described. He gave details as to ligation of various arteries. He cited his own experience and that of others made familiar to him by a thorough search of the literature. Yet one errs if one thinks Hodgson's interests were purely surgical. One of the striking features of the book is that his views were comprehensive. He discussed in a thorough and scientific manner the gross and microscopic pathologic processes in the arterial wall that lead to or accompany aneurysm. He recognized the close relation between lesions seen in the diseased aorta and the coincidental changes in the neighboring valves and coronary arteries of the heart. He submitted some of his experimental work. As an important manifestation of disease of the aortic wall he described cylindric dilatation of the arch without saccular aneurysmal bulging. He referred to the fact that this condition is often seen in those who have had syphilis and raised the old question whether syphilis or the mercury used in its treatment is responsible for the trouble. Today, when the relation of syphilis to a diseased and dilated aorta, often with accompanying aortic valvular incompetency, is better understood, the French frequently refer to the condition as *maladie d'Hodgson*, thus acknowledging the pioneer character of this important work.

One marvels at the scholarly manner in which this book was written, the unusual ability of the young writer of 27 in exposition and argument, the clarity, the purity of his English, the orderly presentation. The frequent summaries are as clearcut, as concise and as logical as a good lawyer's brief. His accurate bibliographic references show that he had made an exhaustive search of the literature of the time.

A separate quarto volume contains the eight plates after drawings by Hodgson. Six were engraved by J. Stewart, two, by J. Shury. These plates were made up of twenty-four figures. The drawings and the engraving, as well as the printed pages of legends, are beautiful examples of the best book making and illustrating of those days.

That Hodgson's interest was not restricted to aneurysm may be seen when one notes a few other topics that he touched on, some very briefly,

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<sup>3</sup> London, T. Underwood 1815

others more fully. He described valvulitis (p 7), postmortem staining (p 8) and aortic regurgitation (p 15). One recognizes in his case III, with its plate and accurate description (p 18), a typical instance of what is today called bacterial endocarditis. He had a clear conception of the interference with function caused by atheroma in the aged (p 24). He depicted the calcareously obstructed aortic valve and contrasted this with mitral stenosis. In the latter condition he recognized a bruit, also a heart pulse that in 1 instance was double that which he felt at the wrist (pp 28-33).

He was familiar with the views of Jenner and Parry as to the relation of angina pectoris to disease of the coronary artery, though his conception of the peculiar substernal distress to which the term angina was applied was not as clearcut as that of Parry, Jenner or Heberden. He recognized the fact that altered coronary arteries may be a cause of heart disease, citing 3 cases in which these vessels were found to be sclerotic and markedly obstructed. Thin-walled ventricles, and in one case rupture, had resulted from this condition (pp 37-40). He described a case of aneurysm of the heart with an intraventricular thrombus, probably from an old infarct (p 84). He recognized what is now spoken of as relative aortic regurgitation (p 50). He offered proof of the rapid compensatory dilatation of minute and previously invisible anastomotic branches in cases of aneurysmal or ligational obstruction (pp 237-238), which recalls the later work of Krogh. He referred to cases reported by others that sound like coarctation of the aorta (pp 250-251). He described phlebitis with the thrombus and drew a striking picture of cases in which septic phlebitis had followed infection at the time of a venesection or in connection with parturition (pp 513-517).

These features of his monograph, especially his description of what is now usually spoken of as syphilitic aortitis (Hodgson's disease), were distinct contributions to the pathogenesis and clinical features of cardiology. They had, and still have, an interest for the nonoperating physician, i.e. the internist.

It is worthy of note that Hodgson made his reputation not in the metropolis, but in provincial Birmingham, the city of his birth. He was known as "Hodgson of Birmingham." Here, for thirty years, he was engaged in an enormous and lucrative general and consultation practice. In 1824 he founded the Birmingham Eye Infirmary. He was regarded as a skilled operator on the eye. He had an enviable reputation as a genitourinary surgeon. He had cut for stone in the bladder 86 times, losing only 4 patients. He was an early advocate of lithotomy. In 1841, with ample means, he withdrew to London. He had no desire to enter further in practice, though he was occasionally consulted by his

patients. He became active in various medical organizations. In 1864 he was president of the College of Surgeons. He died in 1869 at the age of 81, highly regarded by patients and colleagues as a man, a physician and a surgeon.

Some frank comments on his character and ability were made later by Sir William MacCormac in his address of welcome as president of the Royal College of Surgeons at its centenary celebration in 1900.<sup>4</sup> He referred to Hodgson as an able surgeon of the old school. "His diagnosis was accurate but cautious." He was not a brilliant operator. He was averse to innovations, medical or political. In his early life he was constantly involved in many quarrels. In later years he was remarkable for his "suavity and kindness of manner." He was referred to by another, Dr. Madden Stone, as "that mild gentle creature." One may infer that Hodgson was a forceful man, an all-around surgeon of the older, preaseptic school, of an investigative yet skeptical turn of mind, honest and careful and obdurate in defense of his own views. He evidently mellowed as he grew older. One may wonder whether his retirement to London and a quieter life was due entirely to the fact that he had grown tired of the strenuous practice and had accumulated all the wealth he cared for, or whether some sign of ill health warned him to slow up. The obituary notice in the *Lancet* (1869) said he was believed to have had for years a pulse rate of only 40.

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Much has been written of the remarkable group of men who in the first half of the nineteenth century made the Dublin school of medicine take rank close to the schools of Paris and Edinburgh. The internists included Stokes, Graves, Corrigan and Cheyne. They might not be so well known today were it not that their names are attached to certain clinical conditions that were given early and prominent notice by them—Graves's disease, Cheyne-Stokes respirations, Corrigan's pulse, Colles' fracture, Colles' law of syphilis, Stokes-Adams syndrome. Their fame, however, rests on a surer foundation than the fortuitous and fortunate circumstance of having the name attached to a disease or a symptom. These men deserve high rank for their real accomplishments.

Robert Adams (1791-1875), perhaps the least known of the group, was yet held in high esteem by his colleagues as is shown by the fact that he held various hospital and college positions and was three times president of the Royal College of Surgeons of Ireland. He made many contributions to surgery, especially to the surgical knowledge of disease of the joints. In 1873, when he was 81 years old, he brought out *A Treatise on Rheumatoid Gout or Chronic Rheumatic Arthritis*.<sup>5</sup> With

<sup>4</sup> MacCormac, W. Address of Welcome in Centenary of Royal College of Surgeons of England, London 1900 pp. 134-135. *Brit. M. J.* 2:209-212, 1900.

this there was a fine atlas of plates. The writer of an obituary in the *Medical Times and Gazette* referred to him as one highly regarded as a man, "a judicious surgeon," "to be considered as distinguished a physician as he was a surgeon."

The claim to distinction as a physician is based largely on an article of one hundred pages which Adams published in the *Dublin Hospital Reports*.<sup>5</sup> The title of his paper is "Cases of Diseases of the Heart Accompanied with Pathological Observations."

The first description of what is today called the Stokes-Adams syndrome is found in this article. This description has been quoted so often that it need not be repeated here. It clearly warrants one in crediting Adams with having first noted what was later called the Adams-Stokes syndrome. The name of Stokes is properly coupled with that of Adams because Stokes<sup>6</sup> in 1846 in an article in the *Dublin Quarterly Journal* wrote in a comprehensive manner of this type of permanently slow pulse in connection with heart disease. Stokes discussed the relation of all the phenomena to the condition of the heart and spoke of the symptom group as a "combination of a singularly slow pulse, tendency to syncope, and disease of the aortic valve." He concluded by saying that he published these observations made on 7 cases "with the view of drawing the attention of the profession to a combination of cerebral and cardiac phenomena, of which our knowledge is still imperfect."

Robert Adams, however, did much more than describe for the first time and in a somewhat casual manner the peculiar pulse and seizures now called Adams-Stokes syndrome. His article reveals him as possessed of a more than ordinary grasp of the clinical features of heart disease and the associated organic lesions together with the physiologic disturbances accompanying such disease. It is surprising to think that this expertness as a cardiologist was in a sense avocational, for Adams was primarily a surgeon. He represented the type of operator who was first a good all-around physician. Here are some of the features of this article that substantiate the statement.

Several cases of pericarditis were reported. Adams, who was fully aware of the fact that obstruction to the blood current, as from a narrowed valve, leads to increase in the musculature of the heart, said that in an analogous manner obstruction to the free working of the heart because of pericardial adhesions may lead to hypertrophy. But he had a new view as to the cause of such muscular increase.

Although we not unusually find the heart enlarged where the pericardium is adherent to it this has never been, as far as I know, referred to as a cause.

5 Adams, R. *Dublin Hosp Rep* 4 353-453, 1827

6 Stokes, W. *Observations on Some Cases of Permanently Slow Pulse*.  
*Dublin Quart J M Sc* 2 73-85, 1846

its inordinate growth, yet when we reflect that in the natural state the heart has no vascular connexion with the surrounding organs, and is only supplied with two small arteries, we can readily conceive what a new impulse its nutrition must derive from the immense number of vessels which from the adherent pericardium will pass directly into the muscular substance of the heart. Under such circumstances we may fairly attribute enlargement of the heart to the pericardium, as the unlimited growth of a tumour to the organised cyst which contains it.

This, it will be noted, is the basic conception that underlies certain operative procedures of today for improving the circulation in a damaged myocardium by artificially inducing adherent pericardium.

His description of the phenomena of mitral stenosis is such as only a careful and well informed clinician could write. The thrill, the arrhythmia and the pulse deficit are there, the phenomena in the jugular and other veins are described. The essence of King's safety-valve effect in the giving way of the right side of the heart was clearly appreciated. His explanation of the phenomena of the jugular pulse was based on accurate studies of the veins and heart both before and after death. Stokes in his generous way gave Adams credit for having made the first and the most important contribution to the subject of contraction of the mitral valves since the time of Laennec.

Adams came close to, but really missed, recognition of acute coronary obstruction as a cause of myocardial softening. He discussed rupture of the heart muscle, citing a case reported by Dr Cheyne, the symptoms of which would today be recognized as those of coronary thrombosis. The autopsy showed the muscular fiber of the left ventricle "remarkably soft in its structure so as to admit of being broken down between the finger and thumb." Death had been due to hemopericardium caused by a rupture of the wall of the left ventricle through this softened area. Adams cited a second instance of rupture of the ventricle reported by his surgical colleague, the celebrated Abraham Colles.

But Adams came closer than this to discovering coronary thrombosis as the following epitome of his words will show. He presented a masterly discussion of ossification of the aortic valves and contraction of the aortic opening. The thrill and murmur were noted, as were the effects of this lesion on the pulse. He clearly recognized a difference in etiology between aortic obstruction in the young and the old—a juvenile or inflammatory versus a senescent degenerative type. In this connection he reported a case unique in his experience. A fleshy man of 68 had been seized with a severe pain in the chest that ran down the right arm, numbness, dizziness and dyspnea. There was no pulse in the right wrist and a weak pulse in the left. The next day and for seven weeks, or until death, no pulse could be felt in any artery, "an obscure undulating motion could alone be heard when the ear was for some moments attentively applied to the side of the thorax." A diagnosis of heart disease was made, the exact nature unknown.

At the examination made the day after death "the heart was large, flabby and of a yellow color from fatty deposition" The semilunar valves of the aorta were "completely ossified. But this bony or earthy deposition was not confined to the aorta, it extended to the coronary arteries so completely converted into bone as to be quite solid, having no perceptible cavity except at the distance of an inch from their origin, beyond this the vessels were at intervals completely interrupted by small bony specks"

Those present at the dissection were puzzled to understand the symptoms, especially the absence of the pulse, most feeling that the condition of the aortic valves explained all, i.e., that only an insufficient blood supply could get through the narrow orifice. But Adams said that he had seen several other cases of aortic stenosis in which, while the pulse had been small, it was always to be felt. He concluded that some other cause contributed to this effect and believed it was found in the obstructed coronary arteries. He argued that in other muscular organs, if the natural blood supply is cut off, paralysis, partial or complete, follows.

When we reflect that the heart can derive no supply from any other source than its coronary vessels, it will not appear then so extraordinary that partial paralysis should be the immediate consequence of the complete obstruction of these channels upon which the heart is evidently so dependent. The paralysis, if we dare so denominate it, was not in this instance, and indeed seldom is in any case, so complete as to deprive the muscular organ of all power of motion. The heart was still just capable of contracting, and thus passing onwards the blood it received, but so feeble was its impulse that the slightest motion was not perceptible in any branch of the arterial system.

It is evident that there must have been something mechanical in the cause which thus impeded the action of the heart.

A few sentences later he said "The suddenness of the cessation of the pulse precludes the possibility of our accounting for it on mechanical principles." Apparently he meant that there was no permanent mechanical obstruction of the radial or other peripheral arteries. Adams regarded the case as an irregular form of angina pectoris. He concluded "Thus, although we can have but little doubt that in the case we have just been considering the organic seat of the gentleman's complaint was to be found in an ossified condition of the coronary arteries of the heart and aortic valves, we are not by such a consideration furnished with any certain means of knowing why the pulse suddenly ceased in every artery in the body at a time when the general health seemed unimpaired."

One cannot help thinking that had the myocardium been examined more carefully evidence of recent damage might have been discovered. A more thorough search in the coronary vessels would have revealed it.



offending thrombus. As it was, by exceptionally clear, logical reasoning Adams came close to discovering the true nature of cases that today are not so mystifying as they were a hundred years ago.<sup>7</sup>

Adams was far from being a lesser light in the Dublin galaxy. He was of greater brilliancy than has been generally recognized. He had in him the elements of the true clinical investigator and deserves most honorable mention in any history of cardiology.

122 South Michigan Avenue

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7 Some may question the fact that a patient with acute coronary occlusion can live for days with no perceptible peripheral pulse. I am sure, however, that this is possible. I observed 1 case in which no radial pulse could be felt for six or eight hours before death, the patient being quite conscious during this time. In another patient who lived for five weeks after the coronary accident there was never felt during this period more than a rapid, extremely small thready radial pulse. For hours at a time neither the nurse nor the physician could feel it at all.

# INCIDENCE OF SUBSTERNAL AND INTRATHORACIC GOITERS

THOMAS M JOYCE, MD

PORTLAND, ORE

Substernal and intrathoracic goiters differ only in degree. In the present series, when the major portion of a goiter occurred above the sternum, with only prolongations extending below it, the growth was classified as substernal, and when an entire adenoma was below the level of the sternal notch it was classified as intrathoracic. In the past ten years 173 substernal and intrathoracic goiters have been encountered, and during that same period, 1,334 operations on the thyroid were performed, giving an incidence of 12.9 per cent of abnormally situated goiters. Nine of the 173 patients, or 5.2 per cent, had had one or more previous operations on the thyroid gland, varying from eight months to twenty-one years. The recurrence of eight months was undoubtedly present at the time of the first operation, but the recurrence occurring twenty-one years after the first operation may or may not have been present at the time of the first operation. One patient had had three operations within three years for the same symptom—pressure—before being relieved. The first and second operations had removed practically all of the normally situated thyroid without the intrathoracic tumor even being suspected.

## REPORT OF CASES

CASE 1—E. K., a single woman aged 60, was seen in March 1931. She had undergone the menopause at the age of 42.

Thyroidectomies had been performed in June 1927 and June 1929.

The patient had for years been subject to "strangling spells" and headache, especially if she changed her position quickly. She did not become cyanotic but had difficulty in getting her breath. She complained of tenseness and spasm of the chest with these spells. She complained also of a spastic, irritable bowel. She had been under treatment for this complaint for over a year. The blood and the urine were within normal limits, the Wassermann reaction was negative. The blood pressure was 128 systolic and 76 diastolic. The pulse rate was 80. No thyroid tissue was palpable. There were no rales. There was dulness in the upper part of the left side of the chest. The breath sounds were clear. The abdomen was full and tender.

*Roentgen Examination*—The superior mediastinum showed a large tumor mass with displacement of the trachea and the esophagus to the right. The mass had the appearance of a substernal thyroid.

*Diagnosis*—The diagnosis was intrathoracic goiter and spastic colon.

*Course*—The patient was operated on in March 1931. Procaine hydrochloride and ethylene were used. The tumor was attached to the lower pole of the remaining left lobe. In removing the tumor the pleura was opened with a small amount of hemorrhage. One large pack was left in the neck for four days and, removed gradually. There was no bleeding.

A roentgenogram taken on May 1 (fig 1B) showed the lung fields to be clear. There was no substernal shadow. This case illustrates the absolute necessity of roentgen examination in diagnosis. Figure 1 illustrates the condition before and after operation.

The manner of production of substernal and intrathoracic goiters has been a subject of discussion, but with an adenoma from the lower portions of either lobe and considerable pressure above of muscles or a low-lying thyroid gland, it is easy to see this gland develop in the line

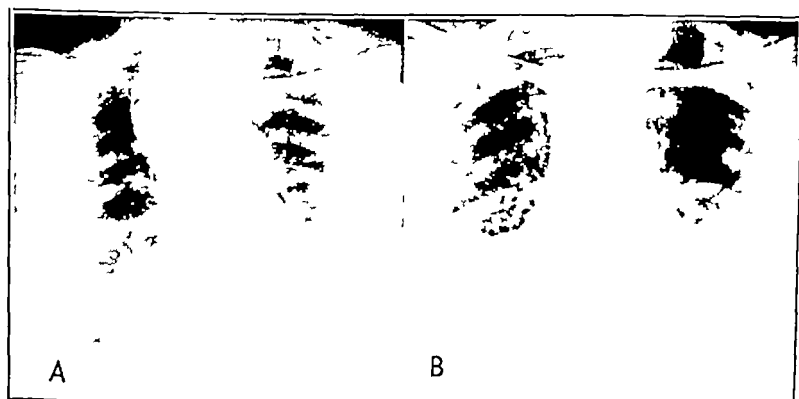


Fig 1—Condition (A) before and (B) after treatment

of least resistance, and after being "hooked" below the sternum it can develop only downward. Also, the influence of swallowing tends to direct the growth downward.

The enlargements were evenly divided as to location, 61 occurred on the right and 60 on the left, with 7 on both sides and no mention made of the situation of the remainder. There was no case, however, in which the intrathoracic extension was completely separated from the lobes above, as with an aberrant thyroid.

#### SYMPTOMS

The predominating symptoms were cardiac disturbances and pressure with dyspnea, husky voice, tumor and enlarged veins (case 2 [not described] fig 2) over the neck and upper part of the chest in the order named (cardiac disturbances to include the cardiac signs incident to the toxic nodular type of goiter). Again, the duration of these symptoms varied from one to forty years. The youngest patient was 17 and the

oldest 78, with an average of 51 years, females predominated, in a ratio of 5 to 1

It is not the size of the tumor which causes the most distress but its location. A small adenoma which will slip up and down under the sternum directly in front of the trachea will cause much more discomfort than an enormous intrathoracic tumor which has room to enlarge without causing pressure on the trachea or on the vessels of the neck. The average amount of tissue removed was 164 Gm, the largest tumor weighing 590 Gm (case 2 [not described], figs 2 and 3). One of these patients, with an intrathoracic tumor on the right, had definite cardio-spasm for which dilation had been done repeatedly. Roentgenograms



Fig 2—Patient in case 2 (not described in text)

of the distal part of the dilated esophagus had not included this intrathoracic tumor, and not until the tumor was removed did the cardio-spasm subside.

Interference with swallowing was a very minor complaint in the series.

Laryngeal displacement and involvement of the vocal cords occurred in 13 patients, or 7 per cent, 3 of whom had been operated on previously and stated that changes in the voice followed operation. There were 10 patients with involvement of the cords who had not had previous operations and undoubtedly the lesion of the vocal cords was due to stretching of the recurrent laryngeal nerve either by displacement

the large vessels in the upper part of the thorax or by displacement of the larynx due to the tumor mass

#### DIAGNOSIS

The diagnosis of intrathoracic and substernal goiters should not be difficult. From the history, the general appearance of the patient, the enlarged vessels, the husky voice, the cyanosis, the position of the larynx and trachea to palpation, the inability to palpate the lower poles of the gland and finally the fluoroscopic and roentgen evidence, one should be able to differentiate these goiters from aneurysm, lymphosarcoma, metastatic growth, lipoma and intrathoracic dermoids.

As is illustrated by case 1, a roentgenogram taken before operation may save the patient either one or two operations.

CASE 3—Mrs W J N, aged 50, was first seen on Sept 25, 1939, on account of palpitation due to an enlarged thyroid. She had been operated on in 1919

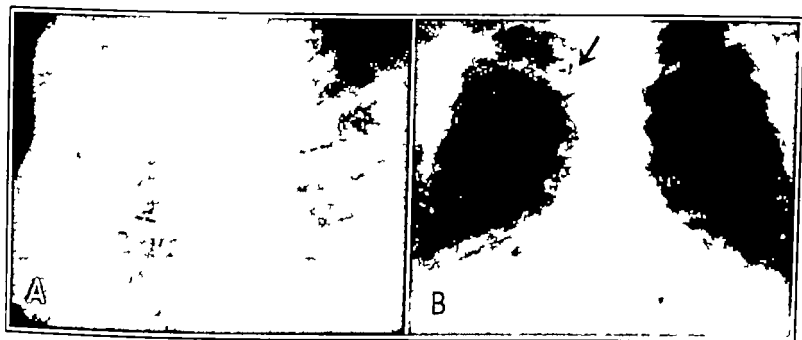


Fig 3—Roentgenograms taken in case 2 (not reported). The amount of tissue removed was 590 Gm. Roentgenogram B shows the result of treatment and indicates the point at which the clavicle was separated from the sternum.

for a large nodular goiter. This started to recur a year later, and in 1932 she was reoperated on. She had had no signs of pressure since her last operation, but her voice had been husky. Her history was otherwise irrelevant.

Examination showed that the left recurrent laryngeal nerve was paralyzed.

Roentgen examination showed a mass in the mediastinum extending down to the level of the sixth thoracic vertebra (fig 4).

The patient was operated on Jan 15, 1940 and the tumor was removed without injuring the right recurrent laryngeal nerve. Recovery was uneventful.

Again, this tumor was not suspected until a roentgenogram was taken shortly before the patient registered at the clinic.

#### OPERATIVE METHODS

Before operation, all the patients are carefully examined by a cardiologist and an internist and kept for from two days to weeks preparing for surgical removal of the tumor.

My anesthesia for years for all goiters has been induced by injection of a local anesthetic agent into the skin and muscles, followed with ethylene. The usual collar incision is used. Twice in this series we have had to separate the clavicle from the sternum (case 2, fig 3*B*) before being able to remove the tumor, and once it was necessary to perform a tracheotomy for compression of the trachea—during operation. The opening in the trachea was closed immediately after the

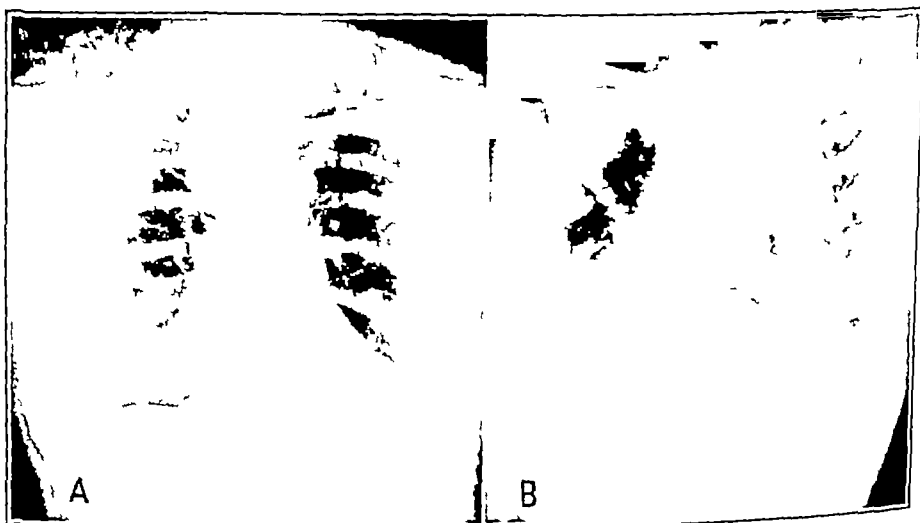


Fig 4—Roentgenograms taken in case 3. *A*, anteroposterior view, *B*, lateral view.

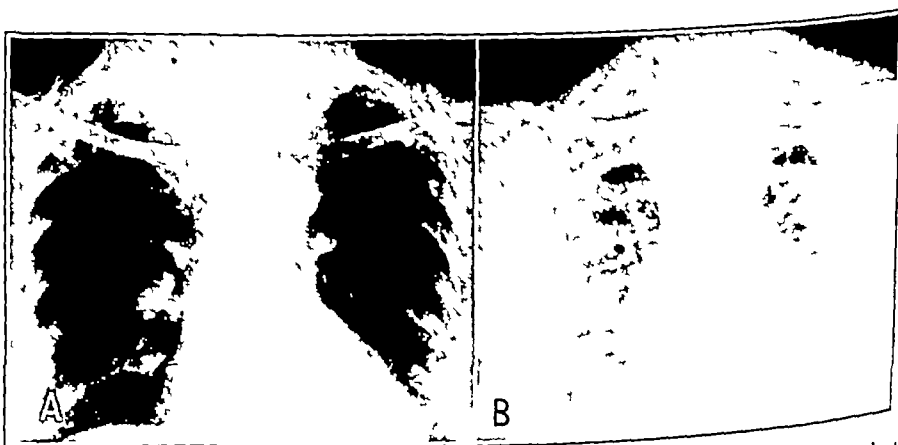


Fig 5—*A*, substernal goiter, showing the displaced trachea (case 4, reported). *B*, bilateral substernal shadow (case 5, not reported).

obstruction was relieved. The tracheal rings have never been noticed to be softened from pressure or displacement with a benign growth, and in my experience only once, years ago, collapse of the trachea. In a case of benign tumor occurred about twelve hours after operation. It was relieved by immediate tracheotomy, recovery of the patient followed.

Soft tracheal rings were noted only in cases of carcinoma of the thyroid with involvement of the trachea. In 3 cases of this series of intrathoracic and substernal goiters there was hemorrhage which from pressure required reopening of the wound and suturing of the gland or packing of the wound open. There were no bilateral nerve injuries, although unilateral paralysis has occurred. (I do not know the exact number of instances, as unfortunately no check was made postoperatively.) I have not attempted to obliterate the cavity from which the tumor was removed but have frequently left a gauze pack in the wound and gradually withdrawn it in from two to five days.

The mortality has been 0.05 + per cent for this group of patients, that is, there was 1 death, which occurred the day after operation from acute dilatation of the heart, and for the total number of thyroids operated on, 1,334, during this ten year period, there were 8 deaths, or 0.05 + per cent.

#### CONCLUSIONS

With care, injury to the laryngeal nerves may be avoided. Absolute hemostasis is necessary. Fluoroscopic study and roentgen plates are essential before secondary operations are undertaken.

# ADENOMYOSARCOMA OF THE KIDNEY (WILMS TUMOR)

## REPORT OF THREE CASES

HERMAN L KRETSCHMER, M D

Urologist, the Presbyterian Hospital, Attending Urologist,  
the Children's Memorial Hospital

CHICAGO

The large number of articles which have appeared during the past ten years on the subject of malignant renal tumors in children is evidence of the widespread interest in this subject. Not only does the urologist regard this subject with deep concern, but the pediatrician, the roentgenologist and the pathologist are equally interested. One of the results of this trend toward intensive clinical and pathologic study of malignant renal tumors on the part of the aforementioned specialists has been the uniform terminology now used in reporting the cases.

In a previous communication<sup>1</sup> I called attention to the fact that these tumors have certain characteristics which the ordinary renal tumors do not possess and that these may be enumerated as follows: 1 Although a few cases have been reported in which the tumor occurred in adults, the fact remains that it is essentially a disease of infancy and childhood. 2 As a rule it runs a silent and rapid course, as is evidenced by the fact that the tumor reaches a large size before medical aid is sought. 3 The histologic picture is unique and singularly characteristic. 4 The outcome is generally fatal. 5 A multiplicity of theories have been advanced from time to time regarding the pathogenesis.

The cause of the Wilms tumor, in common with that of other malignant tumors, is unknown. However, the consensus seems to be that it is congenital. In none of my cases was I able to obtain a definite history of trauma, although in 1 instance the mother thought the child had been injured.

Many theories have been advanced concerning the pathogenesis of this type of tumor, and it may be desirable to review some of them briefly here.

### PATHOGENESIS OF WILMS TUMOR

Eberth<sup>2</sup> gave a very accurate description of a mixed tumor of the kidney. He called attention to the presence in such neoplasms of

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From the Children's Memorial Hospital

1 Kretschmer, H L J Urol 39 250-275, 1938

2 Eberth, C J Virchows Arch f path Anat 55 518, 1872



than one type of tissue and attributed their origin to inclusions of the wolffian body. He attempted to account for the presence of striated muscle on the ground that the connective tissue of the wolffian body is rich in embryonal muscle cells. Later authors pointed out that the embryonal tissue Eberth referred to gives rise to nonstriated but not to striated muscle fibers.

Birch-Hirschfeld<sup>3</sup> expressed agreement with Eberth that these tumors have their origin in the wolffian body. He expressed the belief that such an origin would explain the intimate relation between the tumor and the kidney, without, however, a true blending between the renal substance and the tumor tissue. Later he wrote that the glandular tissue is primary, having its origin in the residual tubules of the wolffian body.

Busse<sup>4a</sup> and Muus<sup>4b</sup> advanced the hypothesis that mixed renal tumors originate from a segregated portion of the renal blastoma, which at some time during its fetal life proliferates and fails to develop normally. The various types of tissue present develop by a process of metaplasia.

Wilms<sup>4c</sup> pointed out that the wolffian body cannot be expected to produce the variety of tissues found in these growths and that they are mesodermal in origin. He assumed that their anlage is a fragment of the primitive undifferentiated mesodermal tissue of the type which in the course of normal development gives rise to the myotome, the sclerotome and the nephrotome.

Herzog and Lewis<sup>5</sup> stated the belief that these tumors owe their origin to an inclusion which is formed when the nephrotome is not cut off at the usual site but is cut off in such a manner that a portion of either the myotome or the sclerotome or both remains in connection with it.

Hinman and Kutzmann<sup>6</sup> called attention to the fact that opinion concerning these embryonic mixed tumors is far from uniform. They stated that it is possible that the simple tumors, or so-called sarcomas, may be explained by Birch-Hirschfeld's theory and the more complex types by Wilms's theory.

Dean and Pack<sup>7</sup> expressed the opinion that, as these tumors may vary markedly in the degree of differentiation of their component cells

3 Birch-Hirschfeld, F. V. *Centralbl. f. d. Krankh. d. Harn- u. Sex.-Org.* **5** 97 1894.

4 (a) Busse, O. *Virchows Arch. f. path. Anat.* **157** 346 and 377 1899.  
(b) Muus, N. R. *ibid.* **155** 401-425 1899. (c) Wilms, M. *Die Mischgeschwülste der Niere*, Leipzig: Arthur Georgi 1899.

5 Herzog, M., and Lewis, D. *Am. J. M. Sc.* **119** 693-701 1900.

6 Hinman, F., and Kutzmann, A. A. *Ann. Surg.* **80** 569-590 1924.

7 Dean, A., and Pack, G. *Embryonal Adenosarcoma of Kidney*. *J. A. M. A.* **98** 10 17 (Jan. 2) 1932.

and in the number of tissues represented, it is evident that they originate at different embryonic developmental periods. The renal blastoma, or nephrotome, is the predominant contributing structure.

Geschickter and Widenhorn<sup>8a</sup> stated that the earlier theories of pathogenesis, relating the Wilms tumor to the wolffian body or to aberrant rests from the sclerotome and myotome, have been superseded by data relating these tumors to embryonic nephrogenic tissue. They stated:

Approximately two-thirds of all Wilms tumors contain only those microscopic elements of spindle cells and early tubule formation which can be found in the normal embryonic kidney or in the zone of development just beneath the capsule of the kidney in normal infants a few months after birth. The majority of these tumors, therefore, are of the normal developmental processes occurring in the growth bones of the renal cortex in late fetal life or in the first few months after birth.

The occurrence of cartilage, bone, or muscle in approximately one-third of these new growths is no strange when we consider that the more undifferentiated mesenchymal spindle cells found in the normal nephrogenic tissue in the process of development may retain the multiple potentiality for the elaboration of all of the normal mesenchymal derivatives.

Ewing<sup>8b</sup> called attention to the fact that "the interpretation of the origin of renal mixed tumors has passed through several phases and covered all apparent possibilities. An origin from an aberrant sex cell has been deemed necessary by Ribbert, who interpreted some of the epithelial rosettes as neuro-epithelium, and who emphasizes the presence of all three germ layers."

I shall present 3 cases of Wilms tumor observed at the Children's Memorial Hospital since the last series of cases was published.<sup>1</sup>

#### REPORT OF CASES

CASE 1—E. S., a white boy aged 1 year and 8 months, was admitted to the Children's Memorial Hospital Dec. 12, 1937.

*Previous History*—The previous history was irrelevant.

*Complaints on Admission*—There had been gradual enlargement of the abdomen and loss of weight for two months, restlessness and irritability for two weeks, diarrhea for the past few days, swelling of the legs for one day and a slight cough for several days. Three days previously the child had had an attack of vomiting, he was always constipated. The mother said that there had been some frequency of urination, but she was very indefinite in her statements.

*Physical Examination*—The child was acutely uncomfortable, with grunting, embarrassed respiration. The head, neck and heart were normal. A few rales were heard at the base of the left lung. The abdomen was enormously distended,

8 (a) Geschickter, C. F., and Widenhorn, H. *Am. J. Cancer* 22: 620-658, 1934. (b) Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 797.

prominent, engorged blood vessels were observed over the front and side of the abdomen (fig 1) The abdomen was very tense and flat on percussion There was a large, hard mass in the left flank, which extended to the pubic area There was marked protrusion of the umbilicus

**Rectal Examination** The lower border of the mass was felt there were definite signs of fluid in the peritoneal cavity

**Blood Pressure** The blood pressure was 80 systolic and 68 diastolic.

**Blood**—Examination of the blood showed red blood cells, 3,100,000 per cubic millimeter, white blood cells 22,500 per cubic millimeter, hemoglobin, 62 per cent,

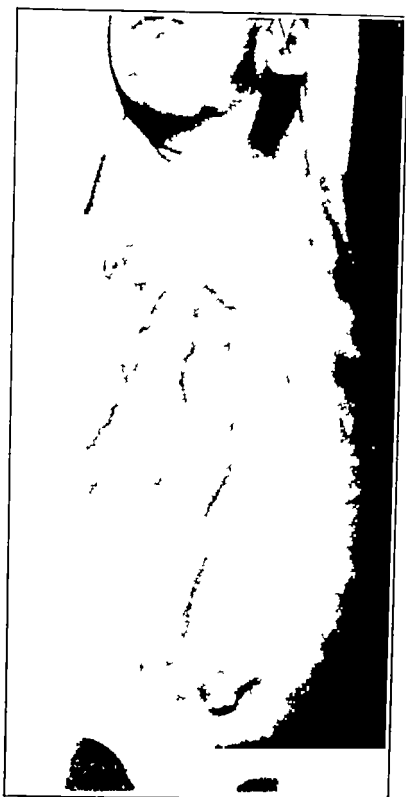


Fig 1 (case 1) —Enormous distention of superficial veins of the abdomen and of the lower part of the chest Note the marked protrusion of the umbilicus

polymorphonuclear neutrophils, 70 per cent, lymphocytes, 27 per cent, eosinophils 1 per cent, and basophils, 3 per cent The Wassermann and Kahn reactions were negative The value for nonprotein nitrogen was 381 mg and that for urea nitrogen 22.2 mg per hundred cubic centimeters

**Urine**—Repeated examinations of the urine gave negative results

**Röntgen Examination**—The chest showed no metastases The diaphragm was elevated A large homogeneous mass nearly filled the abdomen There was lateral and upward displacement of intestinal gas shadows (fig 2-4)

Intravenous pyclograms showed dilatation of the ureter, pelvis and calices of the right kidney (fig 2 *B*). There was only partial visualization of the slightly dilated calices on the left side.

*Abdominal Paracentesis*—On December 13 thick, bloody fluid and a few pieces of tumor tissue were obtained. Histologic examination (Dr W G Hibbs) of these pieces showed the presence of Wilms tumor.

*Treatment and Course*—A course of high voltage roentgen therapy was recommended and carried out. The patient received twelve treatments, consisting of 2,436 r. After the treatment was begun there was some recession in the size of the abdomen, but this was only temporary, and the abdomen gradually increased in size. The child was discharged from the hospital on Feb 28 1938. He died at home on March 21.

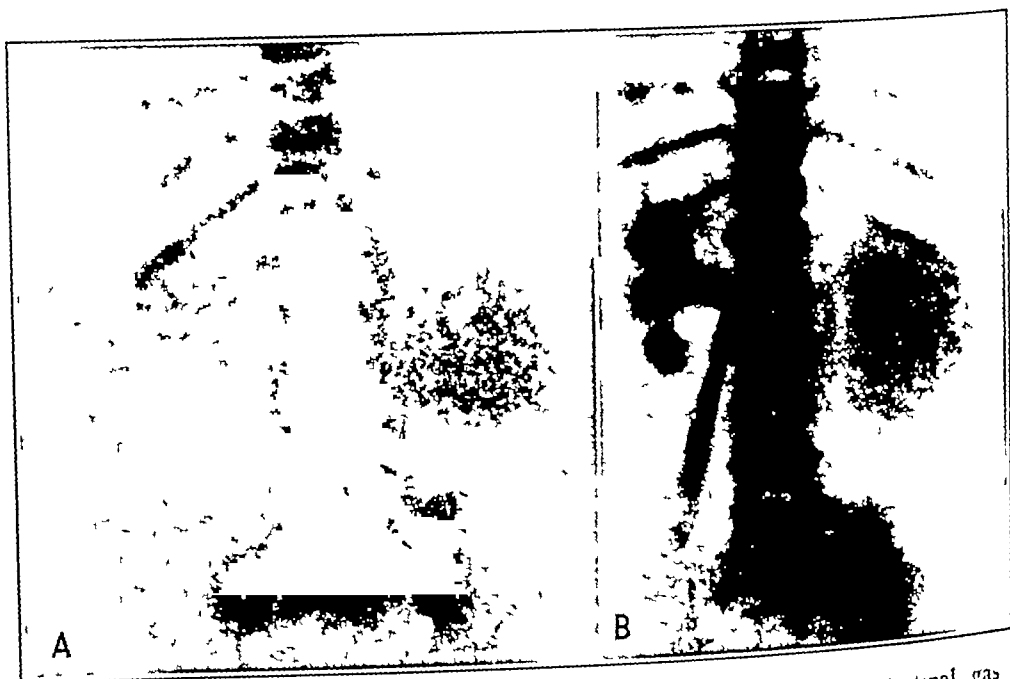


Fig 2 (case 1)—*A*, lateral and upward displacement of the intestinal gas shadows. *B*, dilatation of the ureter and calices on the right side, due to pressure by the tumor. A small collection of dye is seen on the left side.

*Comment*—This case illustrates the fact that not all Wilms tumors show a marked reduction in size after high voltage roentgen treatment.

**CASE 2**—K. C. a white boy aged 2½ years, was admitted to the Children's Memorial Hospital Aug 17, 1938.

*Previous History*—The history was unimportant except for chickenpox in 1937.

*Complaints on Admission*—The mother stated that the child had had some abdominal pain for the past twenty-four hours. She also stated that she had felt a mass on the right side, it had never been noticed prior to this time. On the previous day she had noted for the first time a moderate amount of blood in the urine. All subsequent specimens had shown gross blood.

*Physical Examination*—The boy was well developed and well nourished. The head and neck were normal except for injection and slight bulging of the left ear drum. The heart and lungs were normal. Examination of the abdomen showed

a large, rounded, smooth, hard, nontender mass on the right side, extending to the left of the midline. The mass filled the entire right half of the abdomen. There was no rigidity. The liver and spleen were palpable. The external genitalia were normal. The lower border of the tumor was easily felt with the finger on rectal examination.

**Blood Pressure** The blood pressure was 150 systolic and 95 diastolic.

**Blood**—Examination of the blood showed red blood cells, 5,450,000 per cubic millimeter, white blood cells, 6,000 per cubic millimeter, hemoglobin, 80 per cent, polymorphonuclear neutrophils, 54 per cent, lymphocytes, 42 per cent,

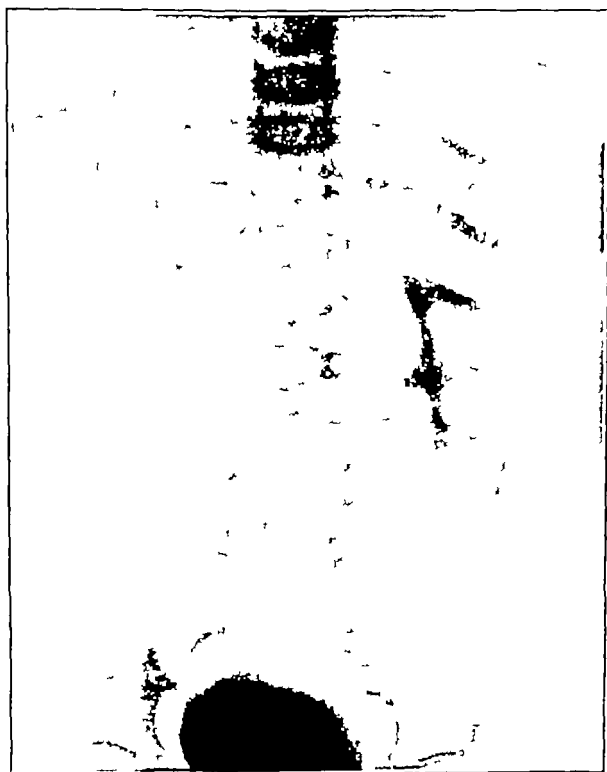


Fig. 3 (case 2)—There is no visualization on the side occupied by the tumor. The opposite pyelogram is normal.

mononuclears, 2 per cent, eosinophils, 1 per cent, and basophils, 1 per cent. The Wassermann and Kahn reactions were negative. The value for nonprotein nitrogen was 38.1 mg per hundred cubic centimeters.

**Urine**—The reaction was acid, albumin was present, there was no sugar. Blood was present, there were many red blood cells and occasional white blood cells, but there were no casts. Repeated examinations of specimens of urine on three occasions revealed blood and red blood cells.

**Röntgen Examination**—The chest showed no evidence of metastases. There were no signs of calculi in the urinary tract. An intravenous pyelogram showed the left side to be normal. There was no visualization of the dye on the right side (fig. 3). A large shadow in the soft parts suggestive of tumor was seen.

The diagnosis was Wilms tumor of the right kidney. A course of high voltage roentgen therapy was instituted, and a total of 3,192 r was given. There was no diminution in the size of the tumor. Operation was advised.

*Operation*—On September 22, with the child under ether anesthesia, the usual oblique lumbar incision was made on the right side, and a nephrectomy was performed.

*Histologic Diagnosis*—The diagnosis was Wilms tumor (Dr W G Hibbs).

*Postoperative Course*—The course was uneventful, and the child was discharged from the hospital on October 14. Postoperative therapy was advised.

*Subsequent Course*—The child died at home very suddenly on Aug 7, 1939. He came in from play complaining of being tired, went to bed and died in one hour.

CASE 3—M W, a white boy aged 7 years, was admitted to the Children's Memorial Hospital Aug 14, 1939.

*Previous History*—The history was unimportant except for an attack of lobar pneumonia in March 1937, followed by complete recovery.

*Complaints on Admission*—There was a large mass in the abdomen. The mother stated that the child had apparently been well, he had not complained. About a week previously she had noticed that the right side of the abdomen was larger than usual and that the umbilicus was more prominent. There were no complaints referable to the urinary tract and no history of hematuria. The child slept well, played heartily and had a good appetite.

*Physical Examination*—The boy was well developed and well nourished, with a sallow complexion and a fine texture of the skin. The head and neck were normal except for the presence of some enlarged, nontender cervical glands. The heart and lungs were normal. The diaphragm was high, especially on the right side. A mass in the right upper quadrant of the abdomen, hard but not tender, extending forward from the region of the kidney to the outer edge of the rectus muscle, was present. The lower edge of the tumor was at, or slightly below, the level of the anterior superior spine of the ilium. The upper edge of this mass, the surface of which was smooth, was separate and distinct from the edge of the liver. The liver was enlarged and extended about 3 fingerbreadths below the costal margin. The veins over the right side of the abdomen and the lower part of the chest were prominent (fig 4).<sup>5</sup>

*Blood Pressure*—The blood pressure was 120 systolic and 90 diastolic.

*Blood*—Examination of the blood showed red blood cells, 4,100,000 per cubic millimeter, white blood cells, 6,900 per cubic millimeter, hemoglobin, 81 per cent. On August 15 the value for nonprotein nitrogen was 44.4 mg, that for creatinine, 1.5, and that for uric acid, 3.8 mg, per hundred cubic centimeters. On September 20 the values were nonprotein nitrogen, 28.2 mg, creatinine, 1.1 mg, and urea nitrogen, 12.2 mg.

*Urine*—The reaction was acid, the specific gravity was 1.024, there was a trace of albumin but no sugar. An occasional white blood cell was seen. Otherwise the urine was normal. Subsequent examinations of the urine during the entire stay in the hospital gave negative results except for one specimen (September 27), which was loaded with pus.

*Roentgen Examination*—A plain film of the abdomen showed no stone in the urinary tract. A large shadow in the soft parts was seen, nearly filling the abdomen. Roentgen study of the chest (August 15) showed the leaves of the

diaphragm to be high. On August 31 a metastatic area in the lung was observed, measuring 2 by 2.5 cm. On September 6, the density appeared slightly larger, the patient had received two roentgen treatments to the chest. On September 15, anteroposterior and lateral views failed to show the oval dense shadow noted previously in the base of the right lung. On September 25 there was no roentgen evidence of a pulmonary lesion or of fluid in either pleural cavity.

On August 16, intravenous pyelograms showed normal conditions on the left and no evidence of the visualizing mediums on the right side. A very large shadow was seen in the soft parts



Fig 4 (case 3) —Enormous distention of the superficial veins extending from the sternum to the symphysis pubis

Cystoscopic study revealed that the bladder and the ureteral orifices were normal. The retrograde pyelogram showed a filling defect compatible with tumor of the right kidney (fig 5).

*Examination of the Abdomen*—On August 24 there was definite enlargement. The veins were more prominent over the lower part of the thorax and the upper part of the abdomen than they had been at the previous examination. There was unmistakable ascites. The umbilicus was very large and protruding.

*Diagnosis*—The diagnosis was Wilms tumor. High voltage roentgen therapy was advised. The patient was given 2000 r.

*Abdominal Paracentesis*—On August 20, 1,300 cc of fluid was removed. Examination for tumor cells gave negative results.

*Course*—On August 29 there was edema of the scrotum. The veins of the upper part of the abdomen and the lower part of the chest were markedly increased in size. The liver was enlarged, hard, irregular and nodular.

On September 10 ascites was noted to be increasing rapidly again. Edema over the chest was less marked. There had been edema of the left leg during the last two days. By abdominal paracentesis (September 12) 2,700 cc. of slightly

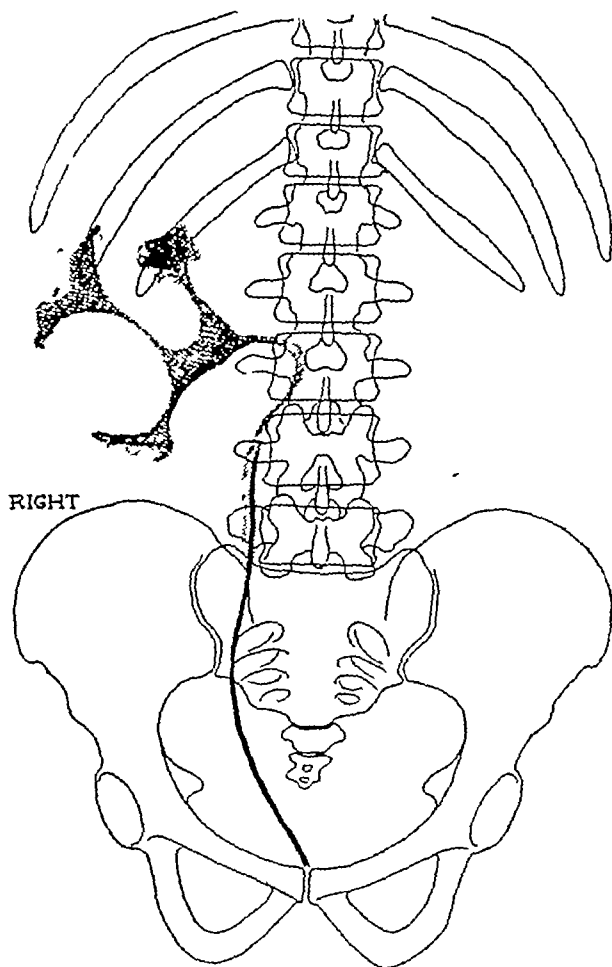


Fig 5 (case 3)—Schematic representation of a retrograde pyelogram, showing a filling defect compatible with tumor.

cloudy straw-colored fluid was withdrawn. Culture of the fluid showed *Staphylococcus albus*.

The patient died on September 29. Postmortem roentgen study of the lungs by Dr. Anspach again failed to show the metastases in the right lung noted on September 6.

In spite of the seeming improvement and the disappearance of the nodular shadows in the roentgen films, the lungs on postmortem examination were riddled with active metastatic nodules.



*Autopsy* (Dr W G Hibbs) —There were embryoma of the right kidney, with direct invasion of the inferior vena cava, adrenal vein, renal vein and right auricle, thrombosis of the left common iliac, hypogastric external iliac and saphenous veins, thrombosis of the right common iliac vein, fibrous adhesions between the tumor, gallbladder, liver and duodenum, duodenal obstruction, metastases in the liver, the lung and the retroperitoneal tissue, congestion of the liver, ascites, edema of the left lower extremity, and right pleural adhesions (fig 6)

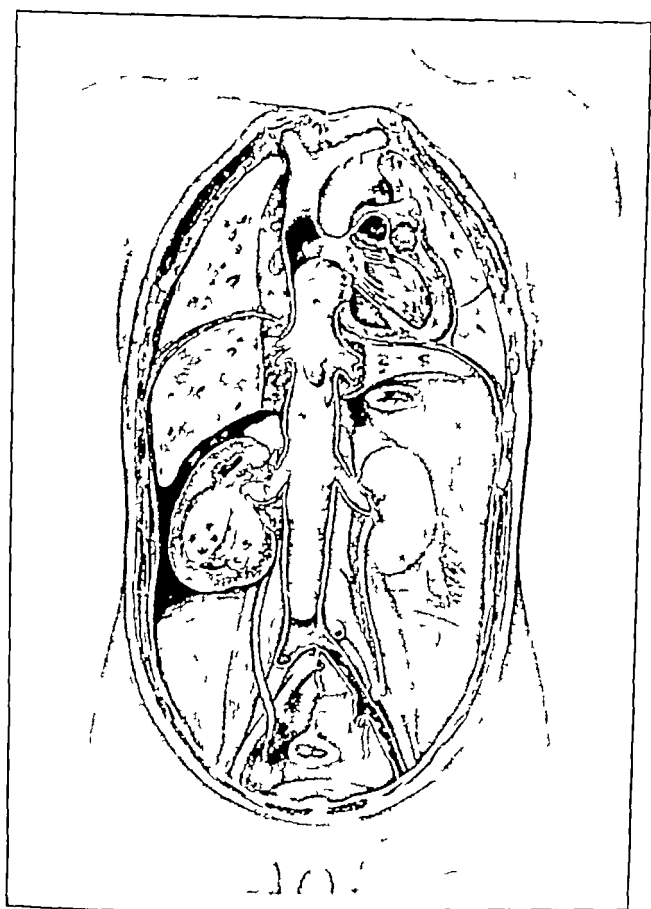


Fig 6 (case 3) —Tumor in the right kidney, with a tumor thrombus in the adrenal vein, both renal veins and vena cava. The tumor thrombus extends into the right auricle

*Comment* —There are three interesting and outstanding facts in this case. 1. After roentgen treatment of the chest, the metastatic nodule seen in the films made September 6 was not demonstrable by the roentgenogram. Roentgen examination of the lungs prior to autopsy revealed no abnormality, yet autopsy showed that the lungs were riddled with metastases. This introduces the question whether a "nega-

tive" film always means absence of metastases to the lung 2 Roentgen therapy failed to cause a reduction in the size of the tumor 3 There was extension of the tumor from the kidney into the right auricle

#### AGE

The Wilms tumor occurs with great frequency in infants and young children In two thirds of my cases the patients were under 4 years of age

Schaffer<sup>9</sup> reported a case in which the tumor occurred in the single kidney of a deformed tetus, and Lubarsch<sup>10</sup> described 4 cases of its occurrence in fetuses and newborn infants Cases have been reported of its occurrence in adults, but they are very rare

#### SEX

The sex incidence is of little aid in the diagnosis In my previous studies<sup>11</sup> 18 patients were males and 6 were females In the 3 cases that form the basis of this paper all the patients were boys It would appear, therefore, that boys are more frequently afflicted than girls (77.77 per cent)

#### GROSS PATHOLOGIC PICTURE

The Wilms tumor is predominately unilateral Bilateral tumors have been reported but they are uncommon I have observed 2 such growths The tumor varies greatly in size The smallest tumor that I have seen weighed 235 Gm The growth may nearly fill the abdomen and extend into the pelvis so that it can be felt on rectal examination This occurred in 2 of the 3 cases reported in this paper There may be displacement of viscera The tumor may take its origin from either the upper or the lower pole or in the middle of the kidney It is encapsulated, it is globular or oval, and it often appears lobulated The surface is generally smooth, although a nodule may protrude above it The kidney is separated from the tumor by a sharp line of demarcation (fig 7) The kidney is compressed by the growth and suffers from pressure atrophy The pelvis also is compressed except in the rare instances in which the tumor seems to grow around the pelvis In my experience the tumor is solid In none of my cases did it have the appearance of a polycystic kidney, although this has been mentioned in the literature

<sup>9</sup> Schaffer, cited by Ewing<sup>8b</sup>

<sup>10</sup> Lubarsch, cited by MacKenzie, in Cabot, H Modern Urology in Original Contributions by American Authors, ed 3, Philadelphia, Lea & Febiger, 1930, vol 2, p 723

<sup>11</sup> Kretschmer, H L, and Hibbs, W G Surg, Gynec & Obst 52 1-24 1931

The tumor may invade the renal vein. In 1 of my cases (case 3) it invaded the renal vein and the vena cava and extended into the right auricle of the heart. Invasion of the heart by a tumor thrombus is very rare (fig 7). In Merkel's<sup>12</sup> case a tumor thrombus extended from the invaded vena cava into the heart.

The cut surface is generally firm and lobulated and varies in color. Dark areas are often present due to hemorrhage within the tumor. In some instances the tumor presents a lobulated appearance due to connective tissue.

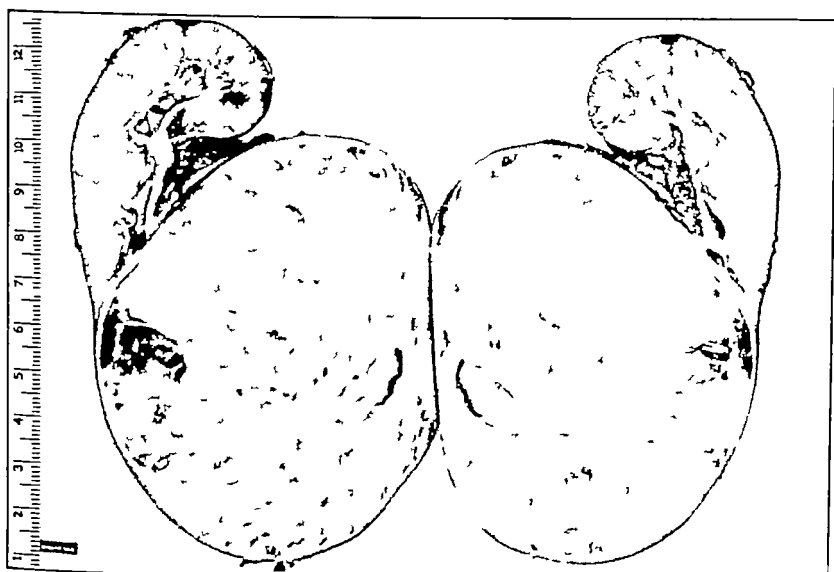


Fig 7 (case 2) —Line of demarcation between the tumor and the kidney. Note the dark area in the tumor, due to hemorrhage.

#### MICROSCOPIC PATHOLOGIC PICTURE

In a previous publication<sup>11</sup> Hibbs and I stated

The embryonal structure of these tumors is their most distinguishing feature with a variety of tissue of abortive renal elements. The types of cells and amount vary in different tumors. They are usually myxomatous tissue composed of masses of polymorphous nucleated cells in which are imbedded gland or duct like figures resembling uriniferous tubules which may be sparse or abundant. These embryonic tubules in a heterogeneous matrix are the most conspicuous features. In addition there are epithelial and connective tissue elements. The connective tissue elements consist of loose stroma, undifferentiated round cells, striated and nonstriated muscle fibers.

<sup>12</sup> Merkel. Beitr. z. path. Anat. u. z. allg. Path. **24**: 475, 1898.

Cartilage and bone cells may be present in some of these tumors, but they are rare and I have never seen them

### SYMPTOMS

It is a well recognized fact that this sort of tumor runs a relatively silent course. As can be readily understood, this is most unfortunate for the patient, since in many cases treatment is sought too late for surgical relief, as was instanced in 2 of the 3 cases reported in this paper. Another drawback is the fact that symptoms referable to the urinary tract are absent, with the possible exception of the rare cases in which hematuria is present. Likewise, pain is a relatively uncommon symptom and occurs late in the course of the disease. Anemia and loss of weight are late manifestations, hence, when the child is brought to the physician because of these symptoms the condition is far advanced. Pressure symptoms, such as nausea, vomiting, constipation and shortness of breath, are also late occurrences.

What is most unfortunate in these cases is that the symptom that most frequently brings the child to the physician is the presence of an abdominal tumor, accidentally noted by the mother or nursemaid.

A palpable tumor was noted in each of the 3 cases reported in this paper. The enlargement was always progressive and painless. The growth varied in size within more or less wide limits, that is, from a small tumor which was just palpable to one which filled or nearly filled the abdomen. In 2 of the cases the tumor extended into the pelvis, so that its lower border was felt with the finger in the rectum. It is rarely if ever, painful on palpation, and the consistency is hard. The surface may be smooth and nodular. In the larger tumors there may be upward displacement of the diaphragm, and in several of my cases the intestines were displaced to the lateral border of the abdomen (fig 2).

### DIAGNOSIS

As a rule the diagnosis presents no difficult problem. The presence of an abdominal tumor which has rapidly increased in size and is hard, sometimes nodular and nearly always painless, coupled with the fact that the commonest abdominal tumor in children is the Wilms tumor, should lead to a tentative diagnosis of that tumor in the case of every child with an abdominal growth.

The diagnosis should be based on the results of a complete urologic study in every case. The plain roentgen examination often reveals a large shadow in the soft parts that in general conforms to the size and shape of the abdominal tumor. But its presence is not pathognomonic of a Wilms tumor, since other retroperitoneal tumors, and occasionally a large hydronephrosis, may cause a similar shadow.

The diagnosis is further strengthened by changes in the pyelogram that are compatible with tumor. In a previous publication, however, attention was called to the fact that in very rare instances the tumor in its growth produces no changes in the pelvis and that therefore the pyelogram may be normal, a fact that should not be overlooked.

In every case in which a tentative diagnosis of Wilms tumor is made, a plain roentgenogram of the chest is taken to rule out the possibility of metastasis, and a plain film of the abdomen is made to rule out stone in the urinary tract. A shadow on the affected side is generally present, and this concurs more or less closely with the size and outline of the tumor. It would be well to bear in mind that a large shadow in the soft parts is not necessarily pathognomonic of a Wilms tumor but may be due to hydronephrosis, neuroblastoma or some other retroperitoneal tumor.

The next step in examination consists of obtaining a set of intravenous urograms. Occasionally there may be complete failure to visualize the renal pelvis on the affected side although the opposite pelvis is shown as normal. But, on the other hand, the pyelogram is frequently most dependable, since it shows a filling defect compatible with tumor. In case the intravenous pyelograms do not yield the desired information, a retrograde pyelogram should be made. Cystoscopic examination, catheterization and functional tests are carried out before removal of the tumor is undertaken.

Failure to visualize the pelvis does not always mean tumor and hence must be checked with a retrograde pyelogram. In 1 case in which a tentative diagnosis of Wilms tumor was made and in which there was no visualization of the pelvis, a retrograde pyelogram was not made. At operation a large hydronephrosis was found.

It is necessary, of course, to rule out other retroperitoneal tumors, such as neuroblastoma, sarcoma and lipoma. At times it may be necessary to differentiate enlargements of the spleen, tumors of the ovary and cysts of the omentum. As a rule these offer no special problem after a complete urologic study has been carried out.

#### TREATMENT

A good many differences of opinion still exist as regards the best form of treatment. McNeill and Chilko,<sup>13</sup> in a survey of 383 cases reported in the literature or observed personally, found that six types of treatment have been followed: (1) nephrectomy alone; (2) the use of serum in conjunction with nephrectomy; Coley having reported a good result from this method; (3) roentgen therapy to reduce the size of the tumor and kill the embryonal cells, followed by nephrectomy; (4)

<sup>13</sup> McNeill, W. H. Jr. and Chilko, A. J. *J. Urol.* **39**: 287-302, 1938.

roentgen therapy followed by nephrectomy and by another course of roentgen treatment, (5) nephrectomy followed by postoperative roentgen treatment in order to destroy any residual malignant embryonal cells, and (6) roentgen treatment alone. They reported the case of 1 patient alive and well three years after irradiation.

Ladd<sup>14</sup> suggested that operation be carried out without delay once the diagnosis has been established.

At present the routine followed by my associates and me is to give the patient a course of high voltage roentgen therapy followed by nephrectomy, after which another course of high voltage roentgen therapy is carried out.

In my experience, not all Wilms tumors are radiosensitive. When the growth is radiosensitive and shows a marked reduction in size, it certainly simplifies nephrectomy.

With the diminution in size of the tumor, corresponding changes are observed in the pyelogram. Attention was called to this phenomenon in a previous publication.<sup>1</sup>

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14 Ladd, W. E. *Ann Surg* **108**: 885-902, 1938.

# FEVER AS INITIAL SYMPTOM OF HYPERNEPHROID TUMOR OF THE KIDNEY

E J McCAGUE, M D

PITTSBURGH

The purpose of this brief paper is to report a case of renal tumor in which the classic triad of hematuria, pain and a palpable abdominal mass was absent. The only clinical manifestation was an obscure febrile state of one year's duration, accompanied with nausea, vomiting and irregular uterine bleeding from multiple fibroids.

## FEVER WITH RENAL NEOPLASIA

The first reference to fever associated with renal neoplasia was made by Israel<sup>1</sup> in 1896. In the case reported by him a man 43 years of age suffered from a hectic remittent fever for several months. At operation a right hypernephroid tumor of the kidney was found. The fever promptly disappeared after removal of the kidney.

In 1911, Israel<sup>2</sup> again commented on the importance of fever as a diagnostic symptom of renal tumor. It was present as part of the picture in 18.3 per cent of the cases that he reported. Concerning the cause of fever he stated: "One does not know what the fever-exciting noxious agent is." Degeneration resulting from bacterial action, which readily plays a part in the causation of gastric, intestinal and uterine tumors, is out of the question with these wholly aseptic tumors of the kidney and adrenal. The cause of the fever must be looked for in the rapid growth of tumor cells or in the destruction of normal tissue. Israel referred to a pyrogenic substance that is elaborated by tumor cells as another possible source of the fever.

Voelcker<sup>3</sup> suggested that the fever in these cases might be the first recognizable symptom of the disease. He thought that the febrile state might be due to the "absorption of albumin bodies produced by the process of involution."

1 Israel, J. Ueber einige neue Erfahrungen dem Gebiete der Nierenchirurgie, *Deutsche med. Wchnschr.* **22** 345, 1896.

2 Israel, J. Fieber bei malignen Nieren- und Nebennierentumoren, *Zentralbl. f. Chir.* **41** 10, 1911.

3 Voelcker, T. Die Neubildungen der Niere, in Kraus, F., and Brugsch, T. *Spezielle Pathologie und Therapie inneren Krankheiten*. Berlin: Urban & Schwarzenberg, 1920, vol. 7, p. 653.

Warburg<sup>4</sup> has shown that tumor cells have a metabolism of their own which differs from that of normal cells. This difference in metabolism between normal and neoplastic cells may cause the change in body economy that produces the variation in temperature.

While the exact cause of the febrile state in cases of renal neoplasia has never been definitely settled, it is believed to be anaphylactic. The fever associated with rapid growth and great size of the renal tumor may be caused by toxic absorption of the products of metabolism of the neoplastic tissues. Foreign proteins are elaborated either by the tumor growth or by central necrosis of the malignant tissue. This material is disseminated by the blood stream. It acts on the thermal centers as a foreign protein, causing anaphylactic elevation of temperature. The fever subsides after the tumor has been removed. When the temperature does not subside after nephrectomy, distant metastases may be suspected.

Fever as an isolated symptom suggesting renal tumor has not been frequently reported in the literature. It may occur irrespective of complicating pyelonephritis. This occurred in the case reported by Nicholson<sup>5</sup>. The patient was a woman 38 years of age who had had an unexplained continuous fever for two years. Even after the most searching and extensive examinations the cause of the fever remained undiagnosed. A renal carcinoma was found at autopsy. Ljunggren<sup>6</sup> (who in 1930 published a clinical and prognostic study of Grawitz' tumors<sup>7</sup>) reported the case of a woman, 52 years of age, with an undiagnosed fever of six months' duration. Urologic investigation revealed a left kidney with the typical characteristics of renal tumor. The patient's temperature became normal and remained so after nephrectomy. Creevy<sup>8</sup> reported 2 interesting cases in which fever played an important part in the clinical picture. The first was that of a patient whose temperature varied between 100 and 102 F for two months. A diagnosis of infected hydronephrosis was made, and the elevation of temperature was explained on that basis. At operation an extensive renal carcinoma was found. The patient remained free from

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4 Warburg, O. Ueber den Stoffwechsel von Tumoren im Körper, *Klin Wchnschr* 5 829, 1926.

5 Nicholson, D. Fever with Renal Carcinoma, *Arch Path* 3 393 (March) 1927.

6 Ljunggren, E. Case of Renal Tumor with Fever as the Only Symptom, *Brit J Urol* 4 249, 1932.

7 Ljunggren, E. Studien über Klinik und Prognose der Grawitzschen Nierentumoren, *Acta chir Scandinav* (supp 16) 66 1, 1930.

8 Creevy, C. D. Pyrexia in Malignant Nephroma, *J A M A* 92 129 (April 13) 1929, Confusing Clinical Manifestations of Malignant Renal Neoplasia, *Arch Int Med* 55 895 (June) 1935.



fever after the operation. It is quite possible that the temperature was due to the renal neoplasia.

Creevy's second case was that of a woman 39 years of age with a low grade fever of several months' duration. She was thoroughly studied, and repeated agglutination tests were made, but no definite information was obtained. She was suspected of having a *Brucella abortus* infection. At autopsy a large necrotic hypernephroma was found. There was no evidence of metastasis.

Castano and Resolia reported a case in which an intermittent fever was the initial symptom of renal tumor. In this case the differential diagnosis included pain, nephric abscess and hydatid cyst of the liver.

In my series of 66 cases of renal neoplasm, fever was present as a complication in 37. In 28 cases the patients were afebrile, in 1 case fever was the only manifestation.

#### REPORT OF A CASE

Mrs C D, a white married woman aged 47 years, complained of weakness, fever, gastrointestinal distress and irregular menstruation. She was admitted to the service of Dr R J Frodey, chief of the gynecologic division, for study and investigation.

The patient had been in her usual good health until approximately one year prior to her admission to the hospital, at which time she began to complain of general malaise and "spells of weakness" accompanied with nausea but no vomiting. Other symptoms, noted at the same time, were moderate dyspnea on exertion and frequent night sweats. The aforementioned symptoms continued, and approximately three months later, four months prior to admission, she began to feel nauseated after meals and frequently would vomit food just eaten. Two months prior to admission the nausea, vomiting and weak spells became more frequent and more severe.

There had been a daily rise in temperature from 99 to 102 F for the past year. One month prior to admission she had been studied by the staff at the Tuberculosis Hospital. They were unable to demonstrate any active pulmonary lesion after exhaustive studies. Roentgen and physical examinations revealed no abnormality. At the time of the study she had leukocytosis, the white blood cell count being 17,750 per cubic millimeter, with 82 per cent polymorphonuclears. For this reason, Dr L H Heatherington suggested further investigation as to some other source of infection.

For the past three years her menses had been irregular in onset, in duration and in amount of flow. The periods had been coming every two or three weeks, and during the past three months she had noticed that the amount of flow had definitely decreased. During the past year she had lost 18 pounds (8.2 Kg) in weight. She had not had any cough pain in the chest or hemoptysis. She had frequently noticed palpitation after exertion. There had been no symptoms referable to the urinary tract. There was no pain, burning, frequency of urination, dysuria, nocturia or hematuria. The past medical history, family history and social history were not contributory.

*Physical Examination*—The patient was somewhat obese. She was nervous. She was resting in bed. The skin was warm and dry. There was no cyanosis, edema or dyspnea.

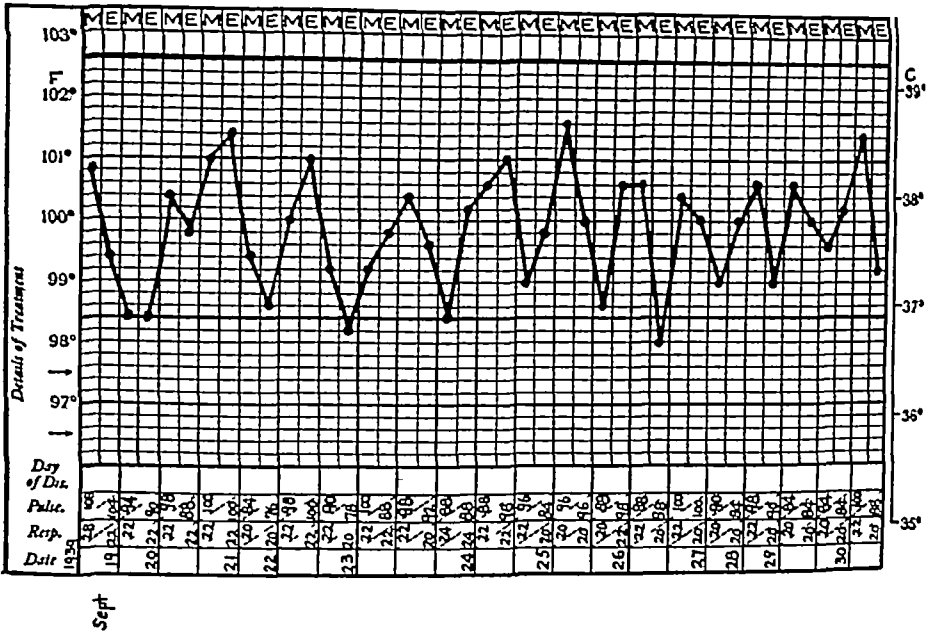


Fig 1—Record of the patient from September 19 to 30. On admission the value for hemoglobin was 60 per cent. The red blood cell count was 3,740,000 and the white blood cell count 8,950 per cubic millimeter. On September 30 a transfusion of 500 cc of citrated blood was given.

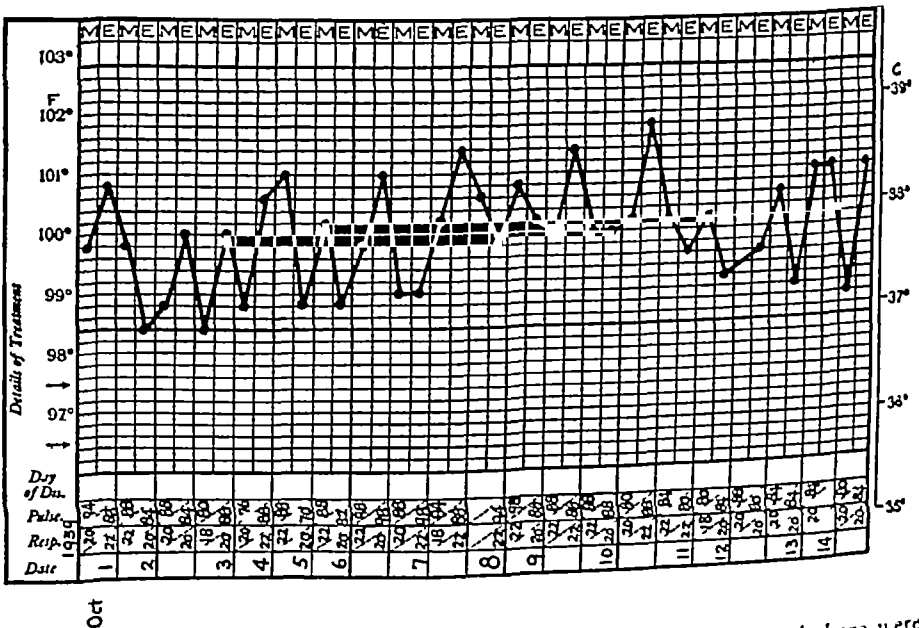


Fig 2—Record of the patient from October 1 to 14. On October 4 there were 4,200,000 red blood cells per cubic millimeter, with 78 per cent hemoglobin. On October 5 a transfusion of 500 cc of citrated blood was given.

The only positive findings were a small firm, nontender mass just above and to the right of the symphysis pubis and a healed low midline incision. The chest was clear. The heart was essentially normal. The blood pressure was 140 systolic and 85 diastolic. The temperature was 100.8 F, the pulse rate was 103 and the respiratory rate was 28.

*Laboratory Studies*—The following data were obtained. The urine was normal on repeated examinations.

The phthaleins ranged between 50 and 70 per cent.

A blood count on September 19 showed red blood cells, 3,740,000 per cubic millimeter, hemoglobin, 60 per cent, and white blood cells, 8,950 per cubic millimeter. Another count, on October 4, showed red blood cells, 4,200,000 per cubic millimeter, and hemoglobin, 78 per cent.

An Ewald test meal on September 26 revealed the value for free hydrochloric acid to be 14, and that for total acid, 30. The blood was normal.

The feces were negative for blood on three occasions.

Macroscopic serologic tests of the blood for typhoid and undulant fever gave negative results.

*Roentgen Studies*—On September 20, roentgen examination after a barium sulfate enema gave essentially negative results except for a soft tissue mass on the right side, not connected with the colon. The right kidney was enlarged.

On October 10 the stomach and duodenum were essentially normal.

*Transfusions*—The patient's blood was of group 2 (Moss). The following transfusions were given:

September 30 500 cc of citrated blood

October 5 500 cc. of citrated blood

October 16 500 cc of citrated blood

*Further Roentgen Studies*—September 25. Investigation up to this point as to nausea, vomiting and the febrile state had not revealed any positive findings. A plain plate of the abdomen at the time of the gastrointestinal studies revealed the right kidney to be somewhat larger than the left, and a request was made that the patient be examined and the status of the right kidney reported.

The lower pole of the right kidney could be felt on deep inspiration. The left could not be palpated. On account of the patient's condition and the fever, intravenous rather than retrograde visualization of the upper portion of the tract was suggested.

An intravenous urogram revealed good function on either side. There was no encroachment on the pelvis or the calices, but there was an enlargement of the right kidney, with a bulging on the lateral side suggesting a renal tumor.

I suggested further roentgen studies of the chest for metastases. This examination was made on September 29.

The report was "Stereoscopic examination of the chest does not show any findings typical of metastatic process."

The question was raised whether the febrile state might be due to degeneration in the uterine fibroids, and Dr. R. J. Frodey, gynecologist in chief, was asked for an opinion.

Dr. Frodey reported "The pelvic organs may be excluded as a possible source of the pyrexia for the following reasons:

1 No tenderness is revealed on palpation of the lower part of the abdomen and bimanual palpation of the pelvic organs.

2 There is no evidence of pelvic exudate in the adnexa or surrounding tissues.

3 Dilatation and curettement exclude possible pyometria or septic endometritis.

4 Some type of degeneration of a fibroid was not likely present as the tumors were all small and not tender, and none were pedunculated."

A diagnosis of right renal tumor and uterine fibromyomas was made and after a further transfusion of 500 cc of citrated blood the patient was operated on (October 17).

*Operation*—Nitrogen monoxide and ether anesthesia was used. The cervix was dilated, and the uterus was curetted. The scrapings were meager and not suggestive of malignant disease. Fifty milligrams of radium (4 to 125 mg needles in a silver capsule covered with rubber) was placed in the uterine cavity to remain for forty-eight hours.



Fig 3—Kidney and tumor

The patient was placed in position for a right nephrectomy. The kidney was exposed through a right lumbar incision, complete dislocation of the kidney revealed a mass at the lower anterior border. A clinical diagnosis of hypernephroid tumor was made, and the right kidney was removed. There was no visible or palpable evidence of extension of the tumor beyond the capsule. The vascular pedicle seemed to be free from extension of the neoplasia.

*Pathologic Report*—The right kidney measured 13 by 9.5 by 8 cm. A mass measuring 9 by 6 by 4 cm projected from the center of the anterior surface of the kidney. The tumor was made up of many small nodules, all of which were

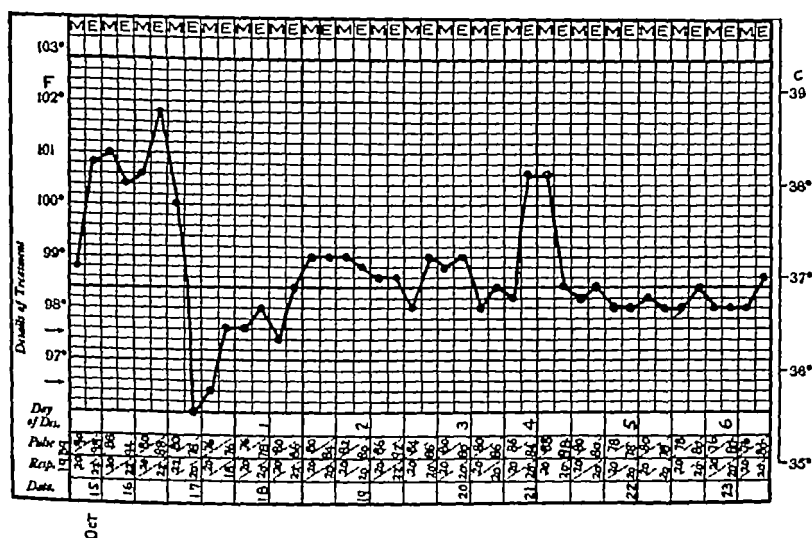


Fig 4—Record of the patient from October 15 to 23. On October 16 a transfusion of 500 cc of citrated blood was given. On October 17 right nephrectomy was performed. On October 18, the radium which had been placed in the uterine cavity at the time of operation was removed. On October 22 the packing was removed.

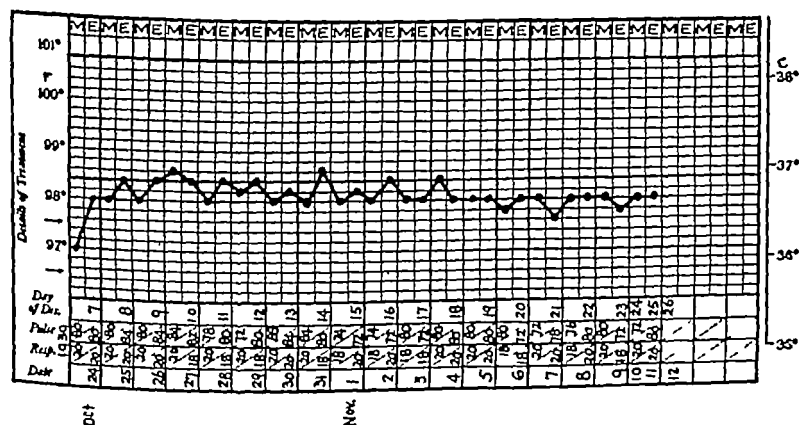


Fig 5—Record of the patient from October 24 to November 12. On October 25 the clips were removed.

entirely encapsulated. On section of the tumor the surface of the neoplastic mass was convex, yellowish red and very soft with a necrotic center. The tumor compressed the pelvis of the kidney but did not invade this structure. On micro

scopic study the essential cell was a large, clear cell, polyhedral to columnar, with a large spindle-shaped polyvesicular nucleus. Both types of mitotic cells were present. The arrangement of the growth was in wide sheets and strands of anastomosing cells. The stroma between the tumor cells was scant, vascular and delicate. A microscopic diagnosis of hypernephroid tumor of the kidney was made. There were no tumor cells in the several pieces of perirenal fat that were submitted for examination. There was no evidence of tumor in the renal vein.

*Postoperative Course.*—The immediate fall in temperature following the nephrectomy and the prompt return to normal were dramatic. On only one occasion in the first four postoperative days did it rise above 99 F. From then on it remained at the normal level until the patient was discharged, on the twenty-fifth postoperative day. The nausea, vomiting and uterine bleeding subsided, and the patient left the hospital free of all symptoms.

#### COMMENT

I think this case of extreme interest by reason of the obscure and unexplained febrile state. Repeated careful investigations as to the usual cause of fever were not enlightening. There was nothing in the history or in the symptoms to suggest the kidney as the source, as the usual symptoms of renal neoplasm were completely absent. It was only when the plain roentgenogram revealed the enlargement that attention was directed to that organ, and urologic investigation indicated the presence of the growth. Its removal was followed by complete subsidence of the fever, nausea and vomiting.

#### SUMMARY AND CONCLUSIONS

A review of the literature shows that fever as the initial and only symptom in renal tumor has been infrequently reported.

Renal tumor should be considered in the differential diagnosis of the condition of any patient who has a protracted and unexplained fever associated with weakness and loss of weight.

Another case of renal tumor with fever as the only symptom is added to the literature.

# GAS GANGRENE

WITH SPECIAL REFERENCE TO THE IMPORTANCE OF WOOL AS A  
SOURCE OF CONTAMINATION

URBAN MAES, M D

NEW ORLEANS

Every great war has always been more destructive than constructive from the medical point of view. However, certain facts have come out of the results of destruction which, when properly evaluated, have done something for the advancement of knowledge. The studies of shock, hemorrhage, compound fractures, thoracic surgery and the care of wounds during the World War have all brought about improvement in surgical treatment. The care of wounds, particularly with regard to infections, is certainly better understood since surgeons have had time to evaluate the accomplishments of surgery since 1918. In the present state of world unrest, surgeons may again be faced with the necessity for studying wounds, particularly with regard to the anaerobic infections.

The history of gas gangrene has been reviewed frequently, and another such account would be superfluous. The incidence of this infection in civil life, the source of contamination and the methods of prevention are more worthy of immediate consideration.

In civil life the incidence of gas bacillus infection is still sufficiently high to warrant some further study of this formidable disease and, in view of the gravity of the infection, further efforts to reduce its morbidity and mortality. The frequency of gas bacillus infection has been reviewed in many recent publications. Callander, Haim and Maximov<sup>1</sup> reported 109 cases, with a mortality rate of 51 per cent, strangely, the death rate from infections of the lower extremity was over 60 per cent and that from infections of the upper extremity only 10 per cent. Ghormley<sup>2</sup> reported 33 cases observed in a five year period at the Mayo Clinic and cited the figures of Millar, who reported a death rate of 48.52 per cent.

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From the Department of Surgery, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana at New Orleans

1 Callander, C L, Haim, A, and Maximov, A. Gas Gangrene. An Analysis of One Hundred and Nine Cases Encountered in Civil Practice, *Am J Surg* 42 811-823 (Dec) 1938

2 Ghormley, R K. Gas Gangrene and Gas Infections, *J Bone & Joint Surg* 17 907-915 (Oct) 1935

during the World War Coller,<sup>3</sup> in a comprehensive review, cited certain French observers as stating that the disease proves fatal in about three fourths of the cases. This was prior to the work of Kelly with roentgen treatment and also to the use of sulfanilamide. Eliason and his associates<sup>4</sup> concluded that the death rate is proportionate to the promptness with which treatment is instituted. The recent report of Mitchell and his associates,<sup>5</sup> who sent a questionnaire to all general hospitals of fifty or more beds in the state of New York, yielded 135 proved cases and 73 more in which the information was incomplete. They concluded from this report that infections with spore bearers that produce gas are as frequent as tetanus.

It is not my intention to go into a detailed study of the pathologic and bacteriologic aspects of this type of infection, as more interest attaches to the clinical aspects. No study of gas gangrene would be complete, however, without some reference to the bacteriologic picture, to the type of wound which favors development of this infection and, in my opinion, to the seasonal incidence of the disease. Laboratory studies have been ably done by trained workers, who have devoted much time and study to these phases of the subject (Pasternack,<sup>6a</sup> Pasternack and Bengston<sup>6b</sup>).

Since the epoch-making studies of Weinberg and Sequin<sup>7</sup> in 1918, one cannot fail to be impressed with the great variety of organisms associated with gas gangrene. From these studies it would appear that the same organisms can produce different phenomena under different cultural conditions. Not only is this true, but the same organism may appear in the literature under different names. According to Pasternack,<sup>6a</sup> "Even such a well-known species as *B. welchii* appears in the

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3 Coller, F. A., and Perham, W. S. Gas Gangrene in Civil Surgery, *Mil Surgeon* **81** 27-38 (July) 1937.

4 Eliason, E. L., Erb, W. H., and Gilbert, P. D. *Clostridium Welchii* and Associated Organisms. Review and Report of Forty-Three Cases, *Surg, Gynec & Obst* **64** 1005-1014 (June) 1937.

5 Mitchell, O. W. H., Bryant, T. L., and Chapman, O. D. Morbidity and Mortality in New York State (Exclusive of New York City) Based on General Hospital Reports for Years 1932-1936 Inclusive, *New York State J. Med* **38** 1022-1025 (July 15) 1938.

6 (a) Pasternack, J. G. The Cardiorenal Toxic Properties of the Toxin of *Vibrio Septique* in Animals, *Am J Path* **14** 683-684 (July) 1938. (b) Pasternack, J. G., and Bengston, I. A. The Experimental Pathological Changes Produced by the Toxin of *Clostridium Histolyticum* in Animals, *Pub Health Rep* **55** 775-784 (May 3) 1940. The Experimental Pathology and Pathological Histology Produced by the Toxin of *Vibrio Septique* in Animals, *Bulletin of the United States Treasury Department, Public Health Service, National Institute of Health*, 1936.

7 Weinberg, M., and Sequin, P. La gangrene gazeuse, Paris, Masson & Cie, 1918.



literature under four names" Most observers, however, seem to recognize a few main groups, and identification of the many subvarieties is dependent on different cultural characteristics *Clostridium welchii*, which is the organism most frequently identified, is placed in the group that requires sugar for its propagation, hence, wounds of muscle and the presence of "muscle sugar" would seem to be favorable factors Some of the other gas producers seem to be proteolytic in their action

Most infections caused by the gas-producing organisms are mixed infections Elason and his co-workers<sup>4</sup> referred to infections with *Cl welchii* and associated organisms The incidence of the various species of clostridia as found in war wounds was best summarized by Gay and his co-workers<sup>8</sup> in 308 war wounds, *Cl welchii* was present in 85 per cent, *Clostridium sporogenes*, in 35.4 per cent, *Clostridium oedematis maligni*, in 17.2 per cent, *Clostridium novyi*, in 12.6 per cent, and *Clostridium fallax*, in 6.4 per cent Since these infections are usually mixed, it is clear that a polyvalent serum would be desirable for prophylaxis and treatment, and such a serum would be difficult to prepare Of course, the predominance of the organism of Welch enables one to concentrate attention on this anaerobe

#### SOURCE OF CONTAMINATION

The matter that has chiefly interested my associates and me in connection with this problem is the source of contamination Most students of the subject agree that soil contamination is an essential factor and that the more highly "manured" the soil the greater is the likelihood of infection This belief is supported by the accepted fact that the organisms are normal inhabitants of the gastrointestinal tracts of domestic animals In this connection I wish to note that in reporting the incidence of various diseases in the Italo-Ethiopian War, Castellani, in his verbal report to the Orleans Parish Medical Society on March 22, 1937, said that there were no cases of gas gangrene In the same connection, the report of Ranson<sup>9</sup> from Shanghai, China, is also striking While his contribution had to do with gunshot wounds of the chest, he said

Although every wound was an infected one, the virulence of the organisms appears to have been less than that of those met with in France and Flanders One reads of the high proportion of cases of gas gangrene and tetanus met with during the Great War, here such cases were comparatively rare

Differences in the bacterial content of the soil doubtlessly account for this The Chinese make use of human excreta for fertilizing purposes, and, although

<sup>8</sup> Gay, F. P., and others. *Agents of Disease and Host Resistance*, Springfield, Ill., Charles C. Thomas, Publisher, 1935

<sup>9</sup> Ranson, F. T. *Notes on Gunshot Wounds of the Chest*. J. Thoracic Surg. 9: 278-290 (Feb.) 1940

this practice fosters the spread of intestinal diseases, soil treated by human excreta is freer from the germ of tetanus and the organisms causing gas gangrene than is soil treated with horse excreta

While all domestic animals harbor the anaerobic organisms, including both the gas producers and the tetanus bacillus, the sheep is a more important source of infection in human beings than are the others, because of the fact that its wool is used for clothing. My associates and I have observed that contamination with woolen clothing is a common source of infection. In 1926, at my suggestion, Gage<sup>10</sup> studied some samples of clean wool and was able to grow spore-bearing organisms in practically all instances. Given a favorable type of wound (muscle injury) and contamination with wool clothing, one has the ideal conditions for development of gas bacillus infection, almost as positively as the small boy who has a punctured wound from stepping on the garden rake presents the ideal conditions for development of tetanus. In this climate the populace dresses in cotton clothing during the hot months, and I have endeavored to show that the incidence of gas bacillus infection is less frequent in the seasons when wool garments are not worn. It must always be kept in mind, however, that contamination with dirt is just as dangerous.

With the assistance of my resident, Dr D B Williams, I have collected the cases from the Charity Hospital in New Orleans during a ten year period, from 1930 to 1939 (table 1) and have analyzed them according to seasonal incidence (table 2) and according to mortality in relation to type of injury (table 3), location of injury (table 4) and type of treatment (table 5).

Our figures show a total of 73 cases of gas gangrene during the ten year period, with 28 deaths, or a mortality of 38.4 per cent. During this same period the number of cases of tetanus was 341.

We have studied the seasonal incidence of the disease because we believe that the wool clothing usually worn in the cooler months is an important source of contamination, but the hospital records usually make no mention of the type of clothing worn by the patient, and we cannot arrive at any definite conclusion. We can assume, however, in view of our experimental findings, that there should be a definite increase in the number of cases in the cooler months, when wool clothing is more likely to be worn, and this is partially borne out by the seasonal incidence shown in table 2.

Following up the studies of Gage at my request, Dr J R Schenken,<sup>11</sup> of the department of bacteriology of the Louisiana State University

<sup>10</sup> Gage, I M. Gas Bacillus Infection. A Frequently Unnoticed Source in Civil Life, with Report of Four Cases, *Am J Surg* 14 177-184 (Oct) 1926

<sup>11</sup> Schenken, J R. Personal communication to the author

TABLE 1—*Incidence of Gas Gangrene According to Years (Charity Hospital of Louisiana at New Orleans)*

Year	Number of Cases	Deaths	Mortality, Per Cent
1930			
1931	10	5	50.0
1932	10	2	20.0
1933	9	4	44.4
1934	8	3	37.5
1935	10	2	20.0
1936	8	4	50.0
1937	5	1	20.0
1938	9	4	44.4
1939	1	1	100.0
	3	2	66.6

TABLE 2—*Seasonal Incidence of Gas Gangrene*

	Number of Cases
December, January, February	16
March, April, May	15
June, July, August	15
September, October, November	27

TABLE 3—*Conditions Complicated by Gas Gangrene (1930 to 1939)*

Condition	Hospital Admissions	Complicated by Gas Gangrene	Due to Gas Gangrene	
			Deaths	Per Cent
Compound fractures	813	23	8	34.8
Gunshot wounds	2,338	23	9	39.1
Crushing injuries	408	13	3	30.0
Gangrene (diabetic and arteriosclerotic)	548	6	3	50.0
Lacerations stab wounds	3,489	4	2	50.0
Other conditions		4	3	75.0
Total incidence of gas gangrene		73	28	38.4

TABLE 4—*Mortality from Lesions of the Extremities in Cases of Gas Gangrene*

	Number of Cases	Deaths	Mortality per Cent
Lower extremity	53	22	41.5
Upper extremity	15	3	20.0

TABLE 5—*Mortality in Relation to Treatment of Gas Gangrene*

Treatment Used	Number of Cases	Deaths	Mortality per Cent
Amputation no serum	11	3	27.3
Amputation plus serum	25	7	28.0
Incisions débridement serum	14	4	28.6
Serum alone	2	2	100.0
Operation serum roentgen therapy	4	1	25.0
Serum roentgen therapy no operation	3	3	100.0
Operation roentgen therapy, serum and sulfanilamide	2	1	50.0
No specific treatment.	6	5	83.0

School of Medicine, has made cultures of some samples of new wool and has submitted the following report to me

*Material and Methods*—Twelve pieces of woolen cloth were obtained from a manufacturer's sample catalog and were cut in half. One half of each piece was dry cleaned and steam pressed, the other half of the same piece was untreated.

Two samples, each measuring 25 by 1 cm, were cut by a cautery from each half piece (48 samples in all). Each sample was inoculated into a separate tube of brain broth, which was then heated in a water bath at 80 C for forty-five minutes. The surface of the medium was covered with a 2 cm layer of sterile melted petrolatum, after which the cultures were incubated at 37 C for fourteen days.

Smears of the broth, stained by Gram's method, were examined microscopically as soon as gas formation was first noted. All positive cultures were later additionally examined to observe spore formation. Two smears of the cultures in which no gas had formed were examined, the first after seven days of incubation and the second after fourteen days.

Samples of cotton, rayon, linen and silk material (12 in all), none of which contained any wool, were obtained from a manufacturer's catalogue and were treated exactly as the woolen samples had been, with cultures made in the same manner.

*Results*—Gram-positive spore-bearing anaerobic gas-forming bacilli, morphologically compatible with the members of the *Clostridium* group, were cultured from one or more of the small samples secured from 11 of the original woolen samples. Cultures of the twelfth sample were sterile. Dry cleaning and steam pressing did not materially alter the incidence of the organism. Gas bacilli were not, however, found in any of the 12 samples of the material which did not contain wool.

This confirms the fact that contamination with clean wool in certain types of wounds should be considered a precursor of gas gangrene. We have observed 2 instances in which gas bacillus infection followed hypodermic injections, 1 instance in which ordinary senile dry gangrene was transformed into gas gangrene and 1 burn that became infected. Interestingly enough, in each of these instances wool blankets had been in contact with the skin or with a raw surface.

The sheep, which has been accused as the domestic animal most likely to be the permanent host of the organisms, is not common in this vicinity, so if one accepts the speculation that wool is the most likely source of contamination one must also note, as is evident from the report of Dr. Schenken, that spore-bearing organisms are present on wool after it has passed through all the processes incident to its final use as a finished garment.

#### TREATMENT

Treatment should be divided into two phases (1) prophylaxis and (2) treatment of established infection.

The best treatment of this disease is prevention of the anaerobic infections, and certain definite rules can be formulated with this end

in view. Once infection with the group of anaerobes capable of producing gas gangrene has developed far enough to be recognizable, a certain mortality is inevitable. However, the therapeutic armamentarium has improved so much in the last few years that physicians do not fear this disease as much as in the past. Certainly, the prophylactic and therapeutic use of serum has done some good, and when one adds treatment with roentgen rays and with sulfanilamide the necessity for radical operation is materially diminished. Some observers go so far as to discount entirely the necessity for amputation and even doubt the advisability of free incision and of treatment with local agents other than the roentgen rays. In reviewing the vast literature of the past few years, one can find enthusiastic advocates of many types of treatment and even statistics to show their value. But judgment must be reserved, for, to quote the editors of the 1939 "Year Book of General Surgery," "Only one hundred years ago the disciples of Benjamin Rush were claiming that practically all diseases should be treated by blood letting."<sup>12</sup> In spite of all methods introduced for treatment of this disease, the mortality is still high, and one cannot evade the fact that prophylaxis for certain types of wounds and early clinical recognition confirmed by bacteriologic examination are the most dependable means of reducing the mortality rate of this disease.

In view of the foregoing statements, it would be wise to consider wounds of the extremities, especially those involving muscle and those contaminated with wool or dirt, as potentially infected with gas gangrene. Wounds of the calf of the leg associated with laceration and devitalization of tissue are especially liable to show subsequent development of organisms capable of producing gas gangrene. Under these circumstances the obvious emergency treatment of such wounds is thorough debridement, with the wound left open, and administration of the antitoxin which is now available, the possibility of secondary closure being kept in mind.

Some recent suggestions by Keating and Davis<sup>13</sup> seem particularly pertinent. These authors suggested the prophylactic use of the roentgen rays for "dirty wounds" as being effective against the gas-forming and other organisms, thereby decreasing the necessity for mutilating surgical procedures.

Should evidence of spreading infection with severe constitutional symptoms develop, the principle indicated by the aphorism of Eliason that the mortality is dependent on the promptness with which treatment is instituted must be rigidly obeyed. While cultures should always be

<sup>12</sup> Graham, E. Year Book of General Surgery, Chicago The Year Book Publishers, Inc., 1939, p. 95

<sup>13</sup> Keating, P. M., and Davis, F. M. Prophylactic Treatment of Wounds in War, *Mil Surgeon* 86: 235-240 (March) 1940

made for confirmation, the delay incident to waiting for such bacteriologic studies may be a determining factor in the patient's life. Usually it takes twenty-four hours to get a report of wound culture, and gas bacillus infections spread so rapidly that twenty-four hours is too long to wait for confirmation of the diagnosis.

The early diagnosis of gas gangrene in civil life dates practically from 1918. Prior to this period the simultaneous appearance of a severe infection and of "gas" in the tissues was the only known sign. As these are antemortem phenomena, the patients were rarely saved by treatment. Amputation of the involved extremities was the only treatment and was always frankly an operation of despair.

Usually the inception of a gas bacillus infection makes itself known by certain local and constitutional changes which should require inauguration of the "curative" measures which are at the physician's disposal. Local swelling and a dry wound with a peculiar odor which has been variously described as a "mousy" or a "rotten meat" smell are significant. The khaki-colored skin in the white race is easily recognized. The patient goes into a state which resembles surgical shock, and even when recovery occurs there is a long period during which the myocardium shows evidence of damage.

Since the work of Kelly and his associates<sup>14</sup> on roentgen treatment, the older procedures have been abandoned by many as unnecessary. The local use of oxidizing agents in the presence of anaerobic infection has been given serious thought. Such agents as potassium permanganate, specific quinine solutions, hydrogen peroxide and pure oxygen have all had their day. Getting these drugs into contact with the organisms without tissue destruction is a "consummation devoutly to be wished," but, considering the method of spread, this cannot be achieved.

In the light of recent experience, the treatment of established gas bacillus infection should be considered under several headings. The curative value of the serum is debatable, but it should always be used. When the work of Kelly and others is considered, one must accept the fact that roentgen treatment lowers the mortality. The report<sup>15b</sup> of a death rate of 11.3 per cent by Kelly and his co-workers certainly represents a decided improvement and gives strong support to the contention that amputations and extensive incisions should be abandoned. According to the observations of Faust,<sup>15</sup> who gives the technic in detail,

14 (a) Kelly, J. F., and Dowell, D. A. Present Status of the X-Rays as an Aid in the Treatment of Gas Gangrene, *J. A. M. A.* **107** 1114-1118 (Oct 3) 1936. (b) Kelly, J. F., Dowell, D. A., Russum, B. C., and Cohen, F. E. Practical and Experimental Aspects of Roentgen Treatment of *Bacillus Welchii* and Other Gas-Forming Infections, *Radiology* **31** 608-619 (Nov.) 1938.

15 Faust, J. J. Report on X-Ray Treatment in Gas Gangrene Cases, *Radiol.* **22** 105-106 (Jan.) 1934.

roentgen therapy causes hydrogen peroxide to be generated in the tissues, and this is the important factor in combating the growth of the organisms and in minimizing generation of the toxin.

The use of sulfanilamide has not been neglected, and, while this drug does not seem to control the specific infection, it may be of value in controlling the growth of the ordinary pyogens, thereby destroying symbiosis. Since the ordinary pyogens use the oxygen present in the tissues and permit the anaerobes to flourish, this effect of sulfanilamide should be of value.

This discussion brings one finally to the value of free incision and amputation. I have always felt that, since spread of the infection is longitudinal, along the muscles, amputation may be advisable to prevent this spread. It is a common observation that in cases in which the calf is involved there is a tendency for the progress of infection to hesitate temporarily at the knee. This interval presents an excellent opportunity for amputation to prevent spread beyond. On account of the arrangement of the musculature about the shoulder, the phenomenon is not observed in this location. I have never resorted to amputation when the arm was involved. Again, even when the infection has been controlled there may be large areas of sloughing, and the patient's recovery may be accelerated by choosing amputation rather than waiting for spontaneous separation of the dead areas to take place. This is especially true of wounds of the leg.

Pasternack has called attention to the susceptibility of the heart muscle to the toxin of vibrio septique, and, as has been noted, the condition of this organ must be watched for a long time even after the patient has recovered from his infection.

#### SUMMARY

Gas gangrene is sufficiently important in civil life for surgeons to give it serious consideration. In conformity with the bacteriologic report of Dr. Schenken, contamination with any woolen article, even clean clothing, makes rigid prophylactic measures imperative. It is urged that physicians suspect anaerobic infection with production of gas gangrene whenever wounds of the extremities involving muscle have been contaminated with wool or with soil. Such wounds should be treated by wide incision (then being left open) or by thorough debridement.

Prophylactic administration of the specific serum seems to be of definite value, and it seems possible from the report of Keating and Davis that the prophylactic use of roentgen therapy is justified.

In the care of a wound in which the factors that favor gas bacillus infection are present, eternal vigilance must be exercised, in the face of suggestive signs of such infection, specific treatment should be started at once. Cultures for confirmation should always be made but the delay

incident to waiting for a report represents valuable time lost. The relative values of the known beneficial factors may be debatable, but since there is some benefit from the anti-gas-bacillus serum and from sulfanilamide and since there is positive evidence of benefit from the use of the roentgen rays, all three should be used. Wide incision and amputation still have their places and must be used when conditions warrant, though the necessity for the use of such measures has materially diminished.

As with all diseases, rules are dangerous, and one must individualize the treatment, making full use of all known beneficial agents.



# GANGRENE OF THE SIGMOID FLEXURE OF THE COLON DUE TO VOLVULUS

RECOVERY OF A CHILD, SPONTANEOUS ANASTOMOSIS BETWEEN  
THE DESCENDING COLON AND THE RECTUM

EDWIN M MILLER, M D

CHICAGO

Acute intestinal obstruction produced by volvulus of the sigmoid flexure of the colon with complete gangrene is very rare in a child, but that such a patient should not only recover but have a spontaneously developed anastomosis between the descending colon and the upper part of the rectum is unique and, therefore, seems worthy of publication

Volvulus, or twisting of the intestines, may occur in any portion of the gastrointestinal tract but is most commonly met with in the sigmoid flexure, the cecum and the ascending colon It is predisposed to by an abnormally long mesentery combined with a narrow base between the afferent and the efferent loops The presence of adhesions and tumors in the mesentery or in the bowel itself is often a contributing factor Constipation unquestionably plays an important role It occurs more often in males than in females, usually affects persons beyond middle life and accounts for perhaps 15 per cent of all forms of intestinal obstruction Children are rarely affected by volvulus, although twisting of the entire small bowel on the axis of the superior mesenteric artery in combination with an incomplete rotation of the cecum in infancy or early childhood may lead to partial or even complete obstruction of the duodenum at its junction with the jejunum

The experience described here has given my associates and me one of the greatest thrills we have encountered in surgical practice

## REPORT OF A CASE

A 12 year old Negress was admitted to the children's surgical ward of the Cook County Hospital at 10 50 p m on Friday, Oct. 13, 1939, with the diagnosis of ruptured appendix with peritonitis The temperature was 101 F the pulse rate was 144, and the respiratory rate was 26 The onset had been acute the patient having been awakened from sleep at 5 a m on October 12 with severe abdominal pain This was followed during the day by nausea and persistent vomiting Magnesium citrate given by mouth and repeated enemas had failed to give her relief On admission to the hospital she looked extremely ill was markedly dehydrated and was begging for something to make her sleep Her abdomen

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From the Surgical Department of the Cook County Hospital

was greatly distended. A Levine duodenal tube was immediately introduced, intravenous fluids were started and enough morphine was given to make her comfortable. The following morning a roentgenogram of the abdomen (fig 1) showed one greatly distended loop of large bowel. The abdomen was silent and tympanic throughout, and a marked bulging was noticed, mostly in the left upper quadrant. At 2 p. m. she was brought to the operating room, and the abdomen was widely opened through a long right rectus incision. A considerable amount of foul-smelling, blood-stained fluid escaped. The entire sigmoid flexure of the colon had been twisted and had become gangrenous. It was so greatly

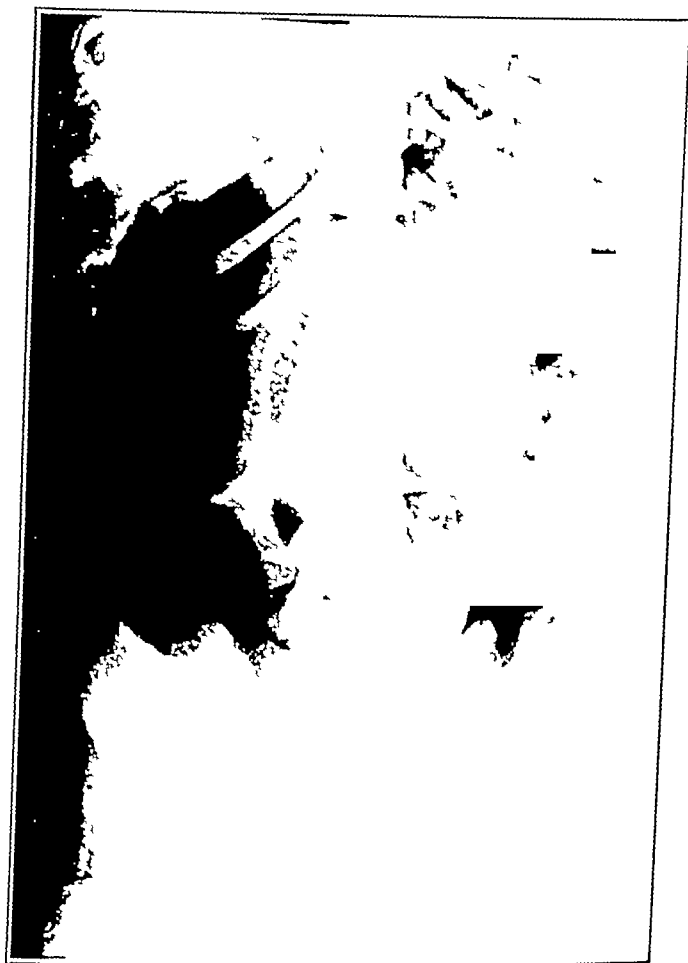


Fig 1—M. M., aged 12 years. There was acute intestinal obstruction due to volvulus of the sigmoid flexure of the colon, with gangrene. The roentgenogram shows the enormously distended sigmoid flexure occupying almost the entire right half of the abdomen.

distended that we were able only with difficulty to deliver it from the abdomen without fear of perforation. Moreover, this gangrenous loop extended so far into the depth of the left flank that resection would have been impossible even if the patient's condition had permitted it. A very conservative plan was therefore adopted. Several strips of petrolatum gauze were gently packed closely about it, the wound was quickly brought together, the huge bowel was slowly deaerated of its foul gas and liquid fecal contents by means of a large syringe, copious dressings were applied, and the child was returned to the ward, every one expecting her to die before many hours had passed.

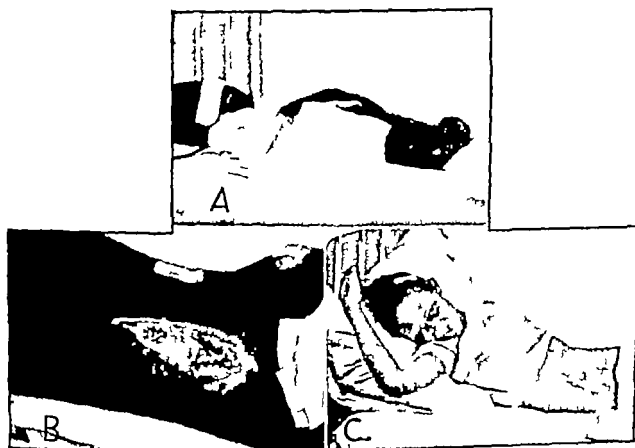


Fig 2—*A*, postoperative color photograph showing the exteriorized gangrenous sigmoid flexure of the colon. *B*, remnant of the sloughing sigmoid flexure at the lower end of the gaping wound. *C*, patient just before leaving the hospital. The continuity of the colon is completely reestablished.



On the following morning, however, the child's condition was surprisingly good, and on Monday (October 16) the exteriorized, greatly distended black bowel (fig 2A) was again deflated by a free incision along the dependent border. On October 17 her condition was excellent, her temperature was lower, and she was asking for food. The Levine tube was removed, and a considerable portion of gangrenous bowel was trimmed off. Steady progress was made from that time on, a little more sloughing tissue coming away each day until by October 24, ten days after the operation, only a small amount of black slough could be seen in the depth of the granulating wound (fig 2B).



Fig 3—Roentgenogram taken after complete sloughing of the sigmoid flexure of the colon, showing the spontaneous channel between the proximal and distal segments of bowel.

The interesting and strange aspect of her progress was first observed on November 11, almost one month after operation, when she passed a normal stool by rectum. Much to our amazement this continued to take place without interruption each day thereafter, the excreta gradually increasing in amount until perhaps one half of the fecal content of the colon was passing through the normal way, thus effectively establishing spontaneously a narrow channel around the opening in the abdominal wound. Before long, however, we began to consider seriously the advisability of more completely reestablishing the continuity of the bowel by operation, and, therefore, barium sulfate was introduced both from above and from below. A roentgenogram (fig 3) made on November 21 gave

us an excellent graphic demonstration not only of the length of the remaining descending colon but of its proximity to the upper part of the rectum, suggesting the feasibility of making a wide anastomosis which would effectively short circuit the area occupied by the colostomy opening in the lower portion of the rapidly healing wound from the right rectus incision. This operation was carried out on Jan 29, 1940, through a clean field on the left side, a lateral anastomosis being easily accomplished without tension on the line of sutures. From then on her progress was very rapid. The wound healed without infection, and as the days went by more and more stools were passed the normal way, and conse-

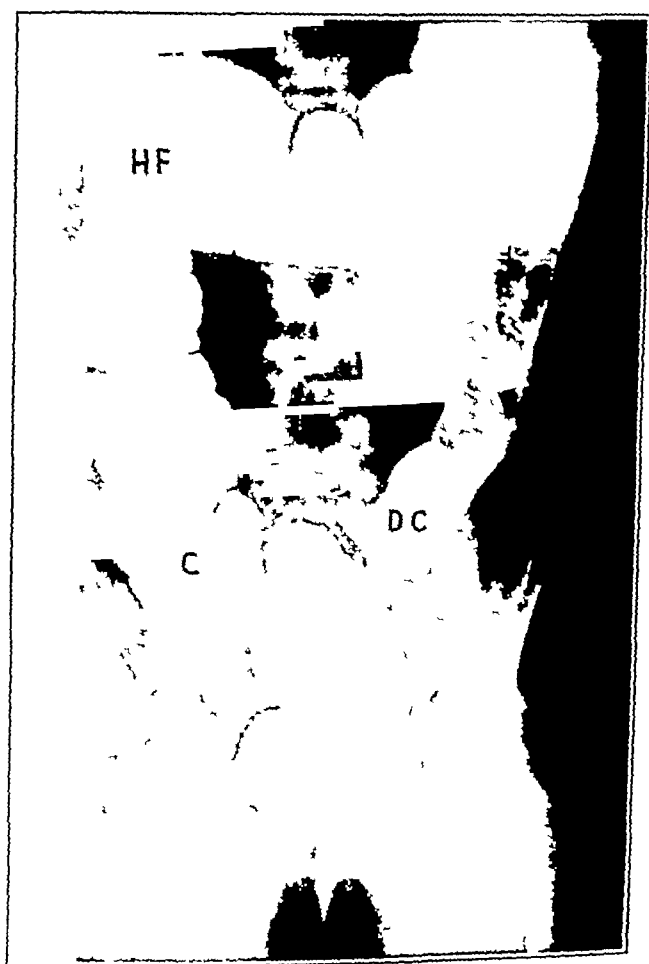


Fig 4—Roentgenogram taken after a barium sulfate enema, showing the continuity of the left side of the colon after the final operation. HF, hepatic flexure, DC, descending colon, C, cecum.

quently less and less fecal material came through the original wound. It therefore became a simple matter to carry out surgically the third and final procedure (February 16), not only completely excising the extensive scar which had resulted from slow healing of the granulating wound and separating the many loops of ileum which had become firmly matted together in this area but securing firm closure of the original incision. The success with which this was accomplished may be realized by a glance at a roentgenogram (fig 4) made March 2, after a barium sulfate enema, and at a "kodachrome" picture (fig 5) of

of the child taken on March 1, just six days before she was discharged to her home, a healthy-looking, happy girl with a normally functioning gastrointestinal tract

#### CONCLUSION

I would emphasize the advisability of being very conservative at the initial operative procedure in the presence of such extensive gangrene and would point out the feasibility of complete reestablishment of the continuity of the left side of the colon

700 North Michigan Avenue

# SURGICAL MANAGEMENT OF SACROCOCCYGEAL AND VERTEBRAL CHORDOMA

CHARLES G. MINER, MD

AND

WILLIAM JASON MINER, MD

BOSTON

Chordoma is so rarely encountered that individual experience is limited, and no clearcut plan of surgical attack on the tumor as it may develop in the different levels of the cerebrospinal axis has been established. A survey of cases reported in the literature reveals a variety of methods of treatment employed, but the results have been far from satisfactory. Sacrococcygeal and vertebral lesions only will be considered in this paper. A procedure will be presented that may permit a more thorough extirpation of lesions in the sacral region, the value of spinal fusion as an adjunct to laminectomy in dealing with vertebral tumors will be discussed, and 3 illustrative cases, heretofore unreported, will be added to the literature.

Chordoma is a tumor arising from the remnant of the notochord. It may occur anywhere in the cerebrospinal axis, from the sphenoid bone to the coccyx. In the order of frequency it is found in the sacrum, the base of the skull and the lumbar portion of the spine, but it may occur in any of the vertebrae. If vertebral in origin, the tumor usually arises in the vertebral body.

Chordomas are difficult to eradicate on account of the usual antevertebral position, the bony origin, the intimate relation to the spinal nerves and, at times, the actual invasion of the dura and spinal cord. Thus block excision is applicable only to the lesions in the sacrococcygeal region, which fortunately are the most numerous. Such tumors should lend themselves to block removal unless they have progressed too extensively, for they usually show a tendency to remain encapsulated, recur locally and metastasize late in the disease. They are of more common occurrence in the lower part of the sacrum or in the coccyx than in the upper segments of the sacrum. Very rarely does invasion of the rectum or of the bladder take place.

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From the Surgical Service of the Beth Israel Hospital and the Neurosurgical Service of the Massachusetts General Hospital



In a compilation of cases of chordoma from the literature<sup>1</sup> Mabrey in 1935 found a total of 150 reported for all levels. Of these, the tumors in 87 were sacrococcygeal. Other cases prior to that date but unreported by him and 32 more to the present time, inclusive of 1 reported in this article, raise the number to 122, in 62 of which the tumors were antedorsal, in 41 retadorsal and in 19 central. Sufficient data for adequate evaluation were available in but 87 of the total number.

By far the great majority of chordomas become manifest between the ages of 40 and 70 years. Men are afflicted twice as often as women. A history of trauma with injury to the lower part of the back or to the gluteal region is obtained in one third of the cases.

Pain is by far the most common and salient symptom and is present in over half the cases. Tumor in the sacral, the gluteal or, less often, the perineal region is frequent. Rectal symptoms, either severe constipation or incontinence, occur in 20 per cent of the patients. Occasionally obstruction supervenes, and very rarely there is bleeding by rectum. Disturbances referable to the urinary tract (incontinence and retention) are somewhat less common, as are referred nerve pains, such as sciatica.

The differential diagnosis of chordoma of the sacrum depends in great measure on roentgen examination, but even with such examination there is room for error at times. One should suspect chordoma whenever a tumor is found which causes severe pain and appears to arise from the sacrum. The tumor may be confused with sarcoma, osteoma, ependymoma of the filum terminale, carcinoma of the rectum with involvement of the sacrum, metastatic carcinoma or tumor arising from the generative organs. One should remember that chordoma seldom ulcerates through into the rectum, though this condition is sometimes reported, as is intestinal obstruction. The tumor is usually smoother, more elastic and more discrete than the malignant tumors just mentioned. Osteoma, on the other hand, is excessively hard.

The roentgen findings may be definitely suggestive. A smooth-walled area of bone destruction, usually near the midline, with a homogeneous soft tissue mass bulging out from the region of the defect, is characteristic. The diagnosis is conclusively established only by biopsy in many instances. The soft gelatinous tumor lends itself to aspiration, and the diagnosis has been frequently proved by this means.

At operation the tumor is very vascular, and after the capsule is entered the mass is usually found to be soft and translucent. It is very

<sup>1</sup> The ultimate result in 3 cases reported by Mabrey is known. The patients in Smith-Petersen and Hampton's case VII and Mixter and Jones case VIII each died of recurrence five years after operation. The patient in Simmons case II died of carcinoma of the uterus nine years after operation. No pathological confirmation of this diagnosis was obtained.

irritable and is slightly yellowish after it is separated from its blood supply. The capsule is a definite structure, and there is a sharp line of demarcation between the tumor and the surrounding tissues. The characteristic picture microscopically, is that of a more or less homogeneous mucoid intercellular substance with widely separated strands or masses of large vacuolated cells. Mitoses are rarely seen.

The three methods of treating chordoma are by irradiation alone, by operation combined with irradiation and by operation without irradiation.

Although occasionally irradiation, either roentgen or radium, may be beneficial, in general the tumor is radioresistant, and little if any improvement may be expected to follow treatment. In 11 cases in which radiation alone was used, no relief was obtained in 7, and only 2 patients lived longer than twenty months, 1 dying with recurrence and metastases in six years and the other in five. Roentgen irradiation and, to a less extent, radium irradiation are valuable as palliative measures in controlling pain.

In 21 of the 87 cases an operation was done, combined with some form of radiation administered either preoperatively or postoperatively. The average duration of life is definitely increased over that observed with the use of radiation alone, but it may be safely assumed that operation was withheld and radiation alone utilized in the cases of most advanced involvement. Mabrey stated that the combined method of treatment gives the best results statistically. This is undoubtedly so, and the 2 cases in which the patients survived for the longest period after institution of treatment both fall into the group in which combined operative and radiation therapy was given. The patient in the case reported by Machulko-Horbatzewitsch and Rochlin died of angina fifteen years after the first operation, at which time coccygectomy with removal of the tumor was performed. In the intervening period three more operations, including excision of the fourth and fifth sacral segments, had been done, and a local curettage was performed some months before death. Roentgen therapy was not instituted until two months before the patient died. In Pool's case the coccyx was excised, and a 3 inch (7.6 cm.) antesacral tumor arising in the sacrum was "removed as completely as possible." The wound was packed open for radium. Nine months later there was a 3 inch recurrent mass palpable through the rectum. The mass remained stationary, and the patient was reoperated on after two years. The tumor was bony hard. No tumor cells were to be seen microscopically. Fifteen years after the first operation the patient was reported to be still alive. It is incontrovertible that irradiation could have played no part in the successful result in the former case, as roentgen therapy was instituted only two months before death. An extensive operation with removal of a large amount of

involved bone was performed in both cases and may well have been the procedure that determined the satisfactory outcome. Yet both of these cases must be included in the group in which combined operative and radiation therapy was used, and in such a small series the exceptional length of survival of 2 patients has a preponderant influence in causing the average period of survival to be the greatest observed in any group.

Operation without irradiation was employed in 55 cases. Thirteen of the patients succumbed after operation. Multiple procedures were done in a number of cases, so that the operative mortality in the 68 operations was 19 per cent. Shock was by far the most common cause of postoperative death, sepsis, pulmonary embolus, peritonitis and thrombosis of the iliac vein were also responsible for fatalities. Colostomy was employed twice, but in neither case as a preliminary stage to a block resection. In 1 instance (Lewis) it was used in conjunction with removal of the tumor through an abdominal approach, and in the other case (Albert) as the third procedure shortly before death occurred.

Reported cases of chordoma have meager follow-up notes, and in many instances the ultimate result is not given. However, there were 9 patients who received operative treatment but no radiation who lived for over three years. In 1 instance (Simmon's case) death occurred from cancer of the uterus nine years after operation on the chordoma. In another (Stewart), recurrence and metastases developed ten years after resection.

From the foregoing considerations it would appear that radical extirpation of sacrococcygeal chordomas offers the best chance of prolonged relief in spite of the high operative mortality of this procedure. We do not know whether it would be feasible to resect the upper two segments of the sacrum. Such an operation would be very difficult and even if successfully carried out would cause great disability. It is possible to resect the sacrum below this level. Such an operation should not be considered if disease of the upper part of the sacrum is too extensive. Careful roentgen examination will determine this. Other contraindications to this type of operation are involvement of the sciatic nerve and evidence of distant metastases.

To diminish the hazard of sepsis at the time of operation and in the postoperative period a preliminary colostomy has many advantages. It should be a defunctioning procedure and yet one that is readily capable of reconstruction should there be no indication for a permanent colostomy after the resection is accomplished. After the abdomen is opened and before the colostomy is done, the peritoneal cavity, the paravertebral lymph node, and liver should be examined for direct extension or metastases. A colostomy of the Devine type established in the sigmoid flexure of the colon permits preoperative cleansing of the distal segment and will relieve obstructive symptoms if present.

As soon as the colostomy is functioning well the sacrum is approached from behind. A block resection is carried out with removal of all the structures involved, including the coccyx and the sacrum to a point definitely above the upper limit of the growth as previously determined by roentgen examination. The first and second sacral nerves will not come into the field of this procedure. One should sacrifice all the lower sacral nerves without hesitation rather than run any risk of cutting into the growth. Preceded removal is to be avoided, not only on account of the danger of recurrence but because of the extreme vascularity of the tumor. The vessels entering these growths are large, and careful hemostasis is important to prevent undue loss of blood. Should resection of the rectum be necessary (a procedure which has been reported in the literature [Senecque and Grinda]) or should injury occur during operation, the preliminary divergence of the fecal stream reduces the danger of serious infection to a minimum.

With a well functioning colostomy and constant drainage of the bladder, the discomfort to the patient is reduced, the after-care simplified by elimination of use of the bed pan and the danger of wound contamination diminished. If the third sacral nerves and all below are cut there will be a considerable area of saddle anesthesia extending forward over the perineum and the external genitalia. There probably will be some loss of function of the anal sphincter but immediate post-operative lack of function is not necessarily permanent. Vesical retention may occur as after any pelvic procedure, and constant drainage is advantageous. Ultimately the sphincter of the bladder should be competent, though too little is known about the exact level of function of the bladder to enable one to be dogmatic on this point. It will be found that the gluteus muscles cannot voluntarily be drawn together after removal of the lower part of the sacrum. The fact that part of the origin of these muscles is left free seems to cause little if any disability.

#### REPORT OF CASES

CASE 1—D. G., a married woman aged 38, was referred to us by Dr. Morris Rutenberg. There was nothing of note in her family or past history. In October 1938 she began having pain low in her back, extending out somewhat into her right buttock. This pain was increased by sitting. It was not associated with urination or defecation. There was no pain or weakness of the legs, and no numbness or paresthesia was observed. The pain was increased by motion and was incapacitating. Examination in December showed a smooth, hard, somewhat tender mass projecting into the presacral space and palpable by rectum. It was not adherent to the rectum and was about 2 cm. across. There was some tenderness of the lower part of the sacrum and coccyx and to the right of the coccyx. Roentgen examination showed a defect in the sacrum, suggestive of chordoma. An operation was performed, the mass being explored from behind and a large amount of new growth removed. A pathologic diagnosis of chordoma was made.

The pathologic report was as follows: Numerous bits of tissue, the largest about 2 cm in diameter, were submitted. Grossly the tissue appeared to be composed of an agglomeration of cysts about 1 mm in diameter. Microscopically, these cystlike areas were seen to represent regions largely composed of mucoid, pale blue-staining, somewhat fibrillary intercellular substance. This characteristic-appearing intercellular substance had embedded in it a variable number of tumor cells, and there was very little other stroma present. The tumor cells were large and stellate, they had indefinite walls and palely staining cytoplasm, often vacuolated. The nuclei were large, pale and somewhat irregular in size and shape, they had prominent nucleoli. Occasional multinuclear cells were observed, but few mitoses.

Roentgen treatment was instituted and continued for several months, at first with some apparent improvement. Then the pain recurred and became more severe than before the operation.

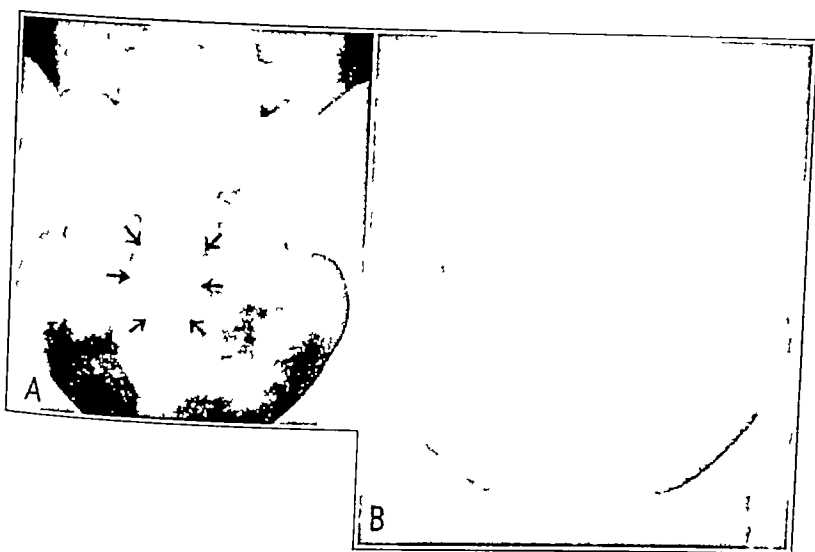


Fig 1 (case 1)—A, roentgenogram taken before the first operation. B, roentgenogram taken two months before the second operation. Note the increase of bone destruction.

When the patient was first seen by us, on Sept 22 1939, it was evident that only radical measures would be of benefit. Her general condition was good but she could do very little, on account of pain. She was taking sedatives regularly but without much relief. She complained of moderately severe constipation, but the function of the bladder was normal. The mass palpable by rectum was now about 6 cm across. The rectum was not adherent to it but was compressed by the mass. The rectal sphincters were relaxed. There was no weakness in the legs and no change in sensation or reflexes anywhere.

The roentgenograms (fig 1) show the progress of the disease during the time she was under observation.

On October 11 a laparotomy was performed. The mass was palpated and it was determined that there was no involvement of the peritoneum, the retroperitoneal lymph nodes or the liver. A Devine type of colostomy was carried out. Con-

valescence from this operation was prolonged by the development of pyelitis. The abdominal wound healed perfectly, and the colostomy functioned well.

On November 29 a second operation was performed. A longitudinal incision was made over the sacrum running nearly to the anus. The greater portion of the sacrum and the coccyx were exposed. The levator muscles and the glutei were cut away and the dissection carried up in front of the sacrum and coccyx. It was remarkable how easily the presacral tissues were separated from the sacrum

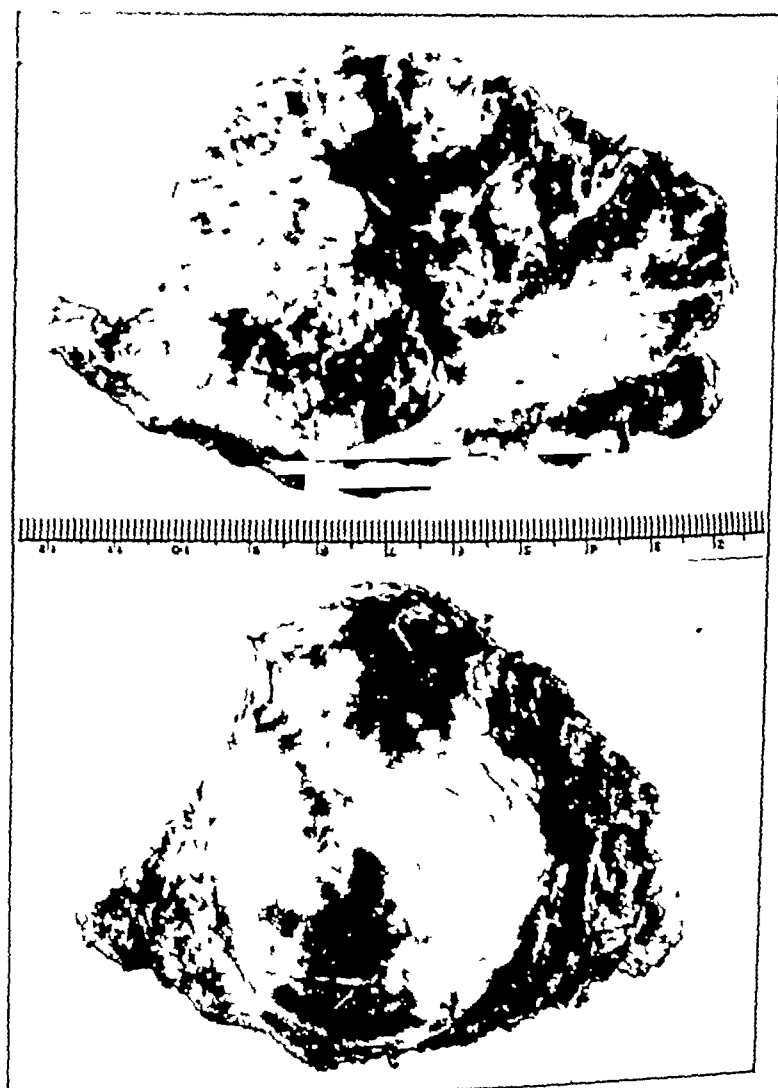


Fig 2 (case 1) —Tumor, portion of the sacrum and coccyx removed in one block

and the mass bulging from it. The dissection was then carried up at the sides of the sacrum, all nerves being sacrificed up to and including the third sacral on the right. It was not necessary to sever the third sacral nerve on the left. The sacrum was dissected free up to the lower edge of the sacroiliac joints. Cuts slanting toward the upper part of the sacrum were made from a little below the sacroiliac joint on each side with heavy cutting forceps, and these were connected across the midline, thus amputating the lower part of the sacrum, the coccyx and the tumor in one block. It was impossible to bring the muscles together

except in part. The superficial fascia and skin were closed, and a moderately large dead space was left, which was drained.

The pathologic report was as follows: The tumor, the coccyx and part of the sacrum had been removed intact and were surrounded by a fibrofatty capsule except over a small area. The bulk of the hemispherical tumor, measuring 8 cm in diameter, was attached to the ventral surface of the coccyx and sacrum, projecting, however, more to the right than the left. The bones were invaded throughout their thickness, the tumor projecting about 1 cm above the dorsal surface. On section the tumor was largely soft and gelatinous, somewhat lobulated, partly necrotic and hemorrhagic and varied from gray to yellowish to brown. Microscopically, the tumor showed less typical intercellular substance and was hence more

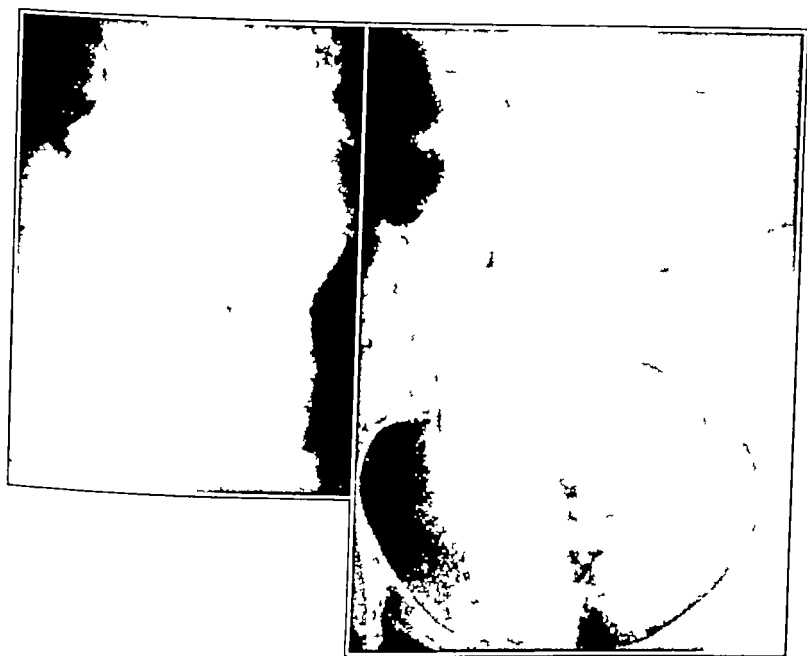


Fig 3 (case 1) —Postoperative roentgenograms showing the extent of removal of the sacrum

cellular. The tumor cells were otherwise similar, but a larger proportion were vacuolated.

As was expected, the wound became infected but finally healed. At first there was retention of urine and constant drainage was carried out. This was unnecessary after a week.

Her condition at the time of writing, five months after operation is satisfactory. She has normal control of her bladder. The right side of the vulva is anesthetic as is an area over the right side of the sacrum and the right buttock. There is no anesthesia of either leg and no change in tendon reflexes. Her gait and station are normal. There is a soft area about the scar on her back that does not give her any discomfort. A colonmetrogram taken by Dr J C White on March 25 1940, shows good sensation and peristalsis in the lower part of the sigmoid flexure and the rectum. The rectal sphincter is continent up to 40 cm of water pressure. The continuity of the sigmoid flexure is now being reestablished.

As was indicated at the beginning of this paper, chordoma of the vertebral column presents a very different problem from chordoma of the lower part of the sacrum and the coccyx. It is rare indeed that a preoperative diagnosis can be made with any certainty. The outstanding features of these growths are similar to those of extradural benign tumor of the spinal canal or of some destructive lesion of the vertebral body. In common with these growths, they usually cause compression of the cord or of the cauda equina with the signs associated with such compression, namely, pain, paralysis below the level affected and block of the spinal fluid. A history of trauma is somewhat suggestive. Chordomas grow more slowly than do malignant lesions. The roentgen picture, while not as characteristic as that of sacrococcygeal chordoma, may be helpful. If the body of the vertebra is involved there may be a rounded cavity visible in it, or there may be an irregular mottled appearance similar to that seen in vertebral hemangiomas except that the mottling is coarser. There is no evidence of new bone formation as in metastatic carcinoma of the prostate, bone destruction is not as intense, nor does it show the moth-eaten appearance characteristic of most of the other forms of malignant disease of the vertebral body. In 1 of our cases (case 3) a presumptive diagnosis of chordoma should have been made by roentgen examination.

The problem of treatment also is different. In the spine one is dealing with a growth which on account of its position is not open to radical extirpation. Therefore, palliative operation and, if desired, roentgen therapy are the only measure. These tumors are of slow growth. There is a definite tendency to dislocation or to collapse of the vertebral body. When the disease is extensive we believe that after exploration and as complete removal of all tumor tissue as is possible, an early fusion operation should be performed to combat this danger. In 1 of our cases (case 2) partial dislocation took place before fusion was carried out. As a result of this experience the other patient was submitted to a fusion operation five weeks after piecemeal removal of the growth. Such an operation adds several weeks to the period of hospitalization. However, the indication for a procedure to strengthen a spine already weakened by this slowly progressive, destructive disease, plus an extensive laminectomy is clearly evident.

CASE 2—J. W. O., a boy aged 14, was admitted to the Massachusetts General Hospital on Nov. 4, 1935. There was no history of unusual trauma to the neck. The patient had always been a strong, active boy.

One year before entrance the patient had had an attack of stiffness in his neck, with pain on motion. This lasted several days. Since that time he had had a number of similar attacks. During the last six months there had been gradual development of numbness and weakness in all four extremities. This began in his right hand and later spread to the left. It was only during the week prior to admission that the process had involved his legs. There had been no pain in



the extremities. Though weak, he could move all the muscle groups. There had been no interference with urination or defecation.

Physical examination revealed nothing remarkable except as follows. There was moderate limitation of motion in the neck, with pain on motion. There were weakness and spasticity of all muscles, including those of the shoulder girdle. Increased tendon reflexes, bilateral Babinski signs and clonus were present. There was diminution of all forms of sensation in both arms. There was no pain or numbness of the occiput.

A combined cisternal-lumbar puncture was performed, which showed evidence of block, and iodized poppyseed oil was injected into the cisterna magna. The

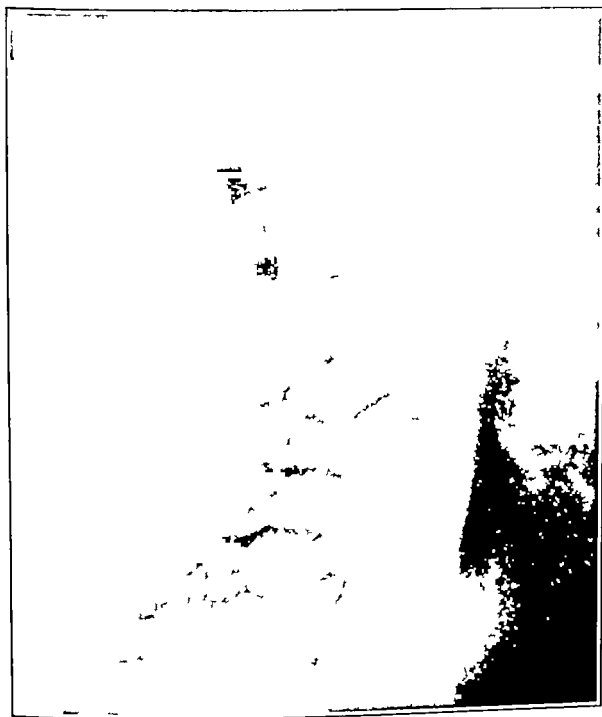


Fig 4 (case 2)—Preoperative roentgenogram. Note the small area of bone destruction in the third cervical vertebra.

total protein content of the spinal fluid from the lumbar needle was 83 mg per hundred cubic centimeters.

Roentgen examination (fig 4) was at first thought to reveal no abnormality but review of the plates at a later date showed a suggestion of bone destruction in the lamina and pedicle on the right side of the third cervical vertebra. Block of the iodized oil, with cap formation, was present at the second cervical vertebra.

Laminectomy on November 16 revealed a soft, reddish extradural tumor lying in front of and to the right of the cord. It seemed to arise from the pedicle and body of the third cervical vertebra and extended from the upper edge of the second to the lower edge of the third. The growth mushroomed out through the second intervertebral foramen. The pedicle and the transverse process were eroded. The

mass was removed in several large fragments the excision apparently being complete except where it seemed to arise from the vertebral body. The right vertebral artery was surrounded by the growth. It was cut across and secured with dura clips.

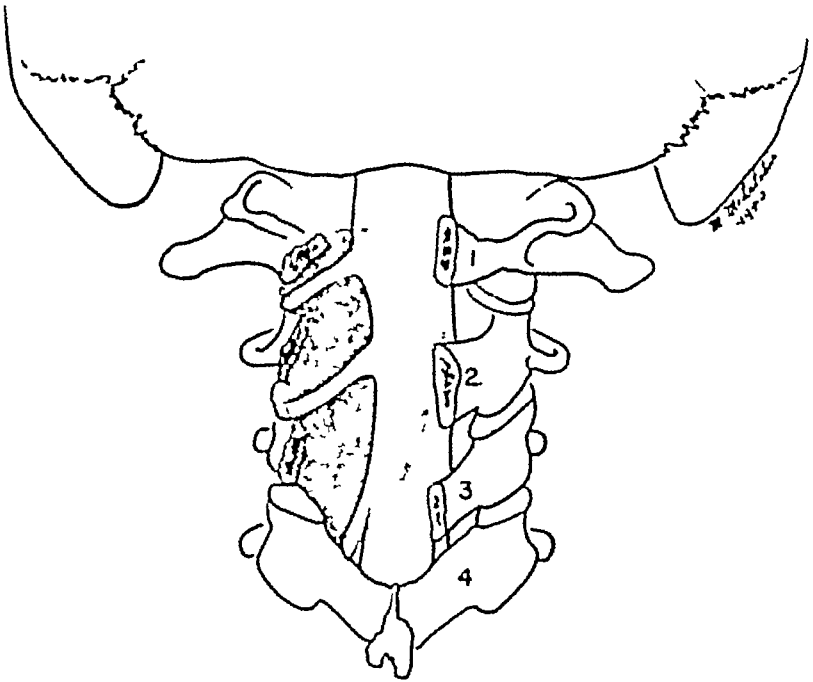


Fig 5 (case 2) —Sketch of the tumor as seen at operation.

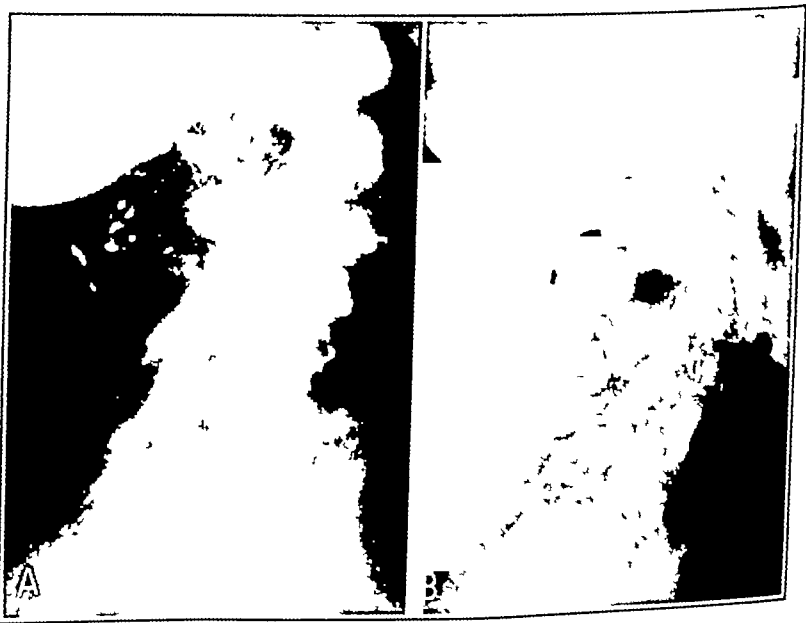


Fig 6 (case 2) —*A*, dislocation following laminectomy. *B*, present condition. Note the reduction of the dislocation and the solid fusion.

Pathologic examination showed the tumor to be a chordoma. No mitotic figures were seen, and it was thought to be of comparatively slow growth.

All muscle weakness, sensory disturbance and reflex changes cleared up rapidly. It was realized that there was great danger of dislocation on account of the bone

destruction and the extent of the operative procedure. Notwithstanding careful immobilization, gradual dislocation took place, though without neurologic signs

The boy was readmitted to the hospital, and a fusion operation was performed on June 16, 1936, by Dr Edwin F Cave

Roentgen therapy was discussed but not advised in this case. It was thought that the tumor was of slow growth and might not recur for many years. It was felt that the massive doses necessary to influence such a growth would be unwise on account of the long life expectancy of the patient.

He has done well in every respect. When seen on Sept 18, 1939, he showed evidence of solid fusion. There was no muscular weakness, impairment of sensation or reflex abnormality. Notwithstanding the fact that his neck is stiff, the boy is running on his school track team. This patient was quadriplegic or rapidly becoming so. The growth was extensive and, together with the wide laminectomy necessary to expose it, weakened his spine sufficiently to cause dislocation.

Correction of the dislocation and fusion have made him a useful and active person with no great handicaps. It is probable that the tumor will recur, but it may not be for some years.

CASE 3—C F B, a man aged 62, was admitted to the Massachusetts General Hospital on Jan 18, 1937

In 1912 the patient fell from the roof of a house, landing on a concrete floor. He was laid up for two weeks with a lame back and left flank. He was bothered off and on for a year by pain in the back. In 1933 he fell 25 feet (7.6 meters), landing on his back. He was unable to stand immediately after the accident, was in bed eight weeks and returned to his work as a carpenter several weeks later. No roentgenograms were taken at this time.

In the spring of 1935 he had pain in his left foot, thought to be from fallen arches.

In November he noticed pain in his left leg and in his back. This increased and was accompanied by weakness beginning in the left leg and later spreading to the right leg. There was no rectal or vesical disturbance. The weakness and pain increased, and when admitted he could barely stand alone.

Physical examination revealed no abnormality except as follows. The lumbar portion of the spine was flat and stiff. There was tenderness of all the lumbar spinous processes. The muscles of the lower parts of both legs were weak, somewhat atrophic and flabby. The quadriceps muscles were of good strength. Sensation was normal everywhere. Knee and ankle jerks were not obtained. Plantar response was down. A lumbar puncture showed evidence of dynamic block and a total protein of 1,380 mg per hundred cubic centimeters. Roentgen examination showed areas of bone destruction in the second lumbar vertebra. Roentgenograms taken after the injection of iodized poppyseed oil showed a cap at the first lumbar vertebra.

Laminectomy was performed on March 17. A soft, reddish tumor mass was found lying in front of the dura and apparently arising in the body of the second lumbar vertebra. It was removed, and a large mass of tumor tissue was scooped out of the vertebral body, leaving a mere shell.

Pathologic examination showed that the tumor was a typical chordoma.

It was felt that a fusion operation was advisable and that roentgen therapy should be carried out.

On April 22, a fusion operation was performed by Dr. William A. Rogers. During convalescence from this operation intensive roentgen therapy was instituted. There was marked tanning of the skin of the back, and a small sinus developed which seemed to run down to the bone graft.

The improvement in the patient's neurologic condition was marked. His pain ceased at once, and the strength in his legs came back gradually.

The sinus has persisted but gives him little trouble and no discomfort.

Examination in March 1940, showed that his back was stiff and severely tanned by irradiation and the presence of the sinus mentioned above. His legs were strong; there was no sensory disturbance anywhere and the reflexes were normal.

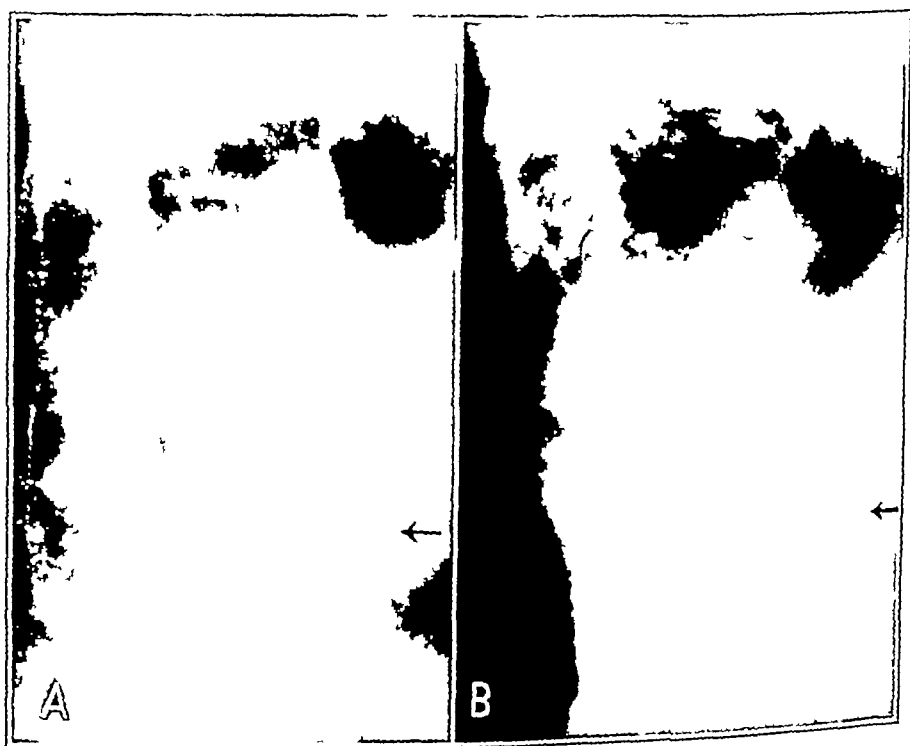


Fig. 7 (case 3)—A, condition before operation. Note the slight enlargement of the vertebral body and the mottled appearance. B, present condition. Note that the vertebral body shows more enlargement and more mottling. Note also the presence of the graft and the straight spine.

Roentgen examination shows increased destruction of the vertebral body at present, but there is no collapse and the spine is straight.

This patient has been put back on his feet and is leading a useful and happy life working as a carpenter. His back gives him no trouble whatever, aside from a tiny dressing over the sinus.

It was felt at the time of his operation that there was great danger of collapse of the shell of the vertebral body.

It is evident that the disease is progressing and will ultimately cause his death. The fusion and possibly roentgen therapy have increased his usefulness and life expectancy.

## SUMMARY

The results of treatment of spinal and sacrococcygeal chordoma have been unsatisfactory

A method of dealing with suitable sacrococcygeal chordomas by a two stage block resection is described

The value of fusion after palliative removal of vertebral chordoma is pointed out

Three hitherto unreported cases of chordoma illustrating these points are reported

In the preparation of this study, Dr Samuel Lowis made a careful study of the cases reported in the literature.

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# SOLITARY NONPARASITIC CYST OF THE LIVER IN CHILDREN

ALBERT H. MONTGOMERY, M D  
CHICAGO

Solitary nonparasitic cysts of the liver are rare, especially in children. In only 25 of the 108 cases reported to date<sup>1</sup> did the lesion occur in children under 13 years of age.

Stoesser and Wangensteen<sup>1a</sup> in 1929 and Wikle and Charache<sup>1b</sup> in 1936 reviewed the literature in detail and reported cases of their own. Little has been added to knowledge concerning these cysts since then. Because the 2 children with this rare condition that have come under my observation exhibited some unusual features, I have thought it worthwhile to report their cases and to comment on the subject.

## REPORT OF CASES

CASE 1—C. D., a white girl aged 6 years, of Irish parentage, was admitted to the Children's Memorial Hospital on Oct. 31, 1935 because of a large, flabby abdomen and an abdominal tumor, both of which had been present since birth. When the child was born the tumor mass was described as firm but movable and about the size of an orange. It was located in the right upper quadrant. The skin of the abdomen at that time was flabby and wrinkled. As the child developed, the size of the mass remained unchanged, but the abdomen had become more pendulous and flabby, without much muscle tone (fig. 1). The birth history, past development and family history were essentially irrelevant. There had been no complaints referable to any system.

*Physical Examination (Positive Findings Only)*—The cephalic portion of the chest appeared flattened and narrow in its anteroposterior diameter. Below the level of the fifth ribs anteriorly there was a definite Harrison's groove, with marked flaring of the ribs on both sides. Inspection of the abdomen with the child lying flat on her back revealed a sunken, somewhat wrinkled skin with a noticeable linear wrinkle down the midline. The umbilicus was definitely to the left of the midline. The left flank had a normal contour, but the right flank seemed to have no muscle tone and bulged laterally. The superficial veins of the abdomen were prominent and appeared to sink into the subcutaneous tissue. With anterior flexion of the head on the neck, there was a visible contraction of both rectus abdominis muscles, the left being more prominent than the right. Both appeared hypoplastic. There was retraction of the upper, middle and lower

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From the Surgical and Pathologic Services of the Children's Memorial Hospital

1 (a) Stoesser, A. V., and Wangensteen, O. H. Solitary Nonparasitic Cysts of the Liver, *Am J Dis Child* **38** 241 (Aug.) 1929. (b) Wikle, H. T., and Charache, H. *Am J Surg* **31** 345, 1936.

segments of the left rectus muscle when the skin in that region was stimulated, but no response was seen on the right to a similar stimulation. The oblique muscles of the abdomen appeared normal on both sides.

The abdomen was flabby and doughy, and its contents were easily palpable. In the right upper quadrant, situated well under the ribs, was a firm, hard, round mass approximately 7 cm in diameter. The tumor was freely movable and fell into the false pelvis when the child was erect.

When the child stood there was a falling forward of the abdomen in a pendulous, atonic protuberance, strongly suggesting the appearance of a post-partum abdomen in a multiparous woman.

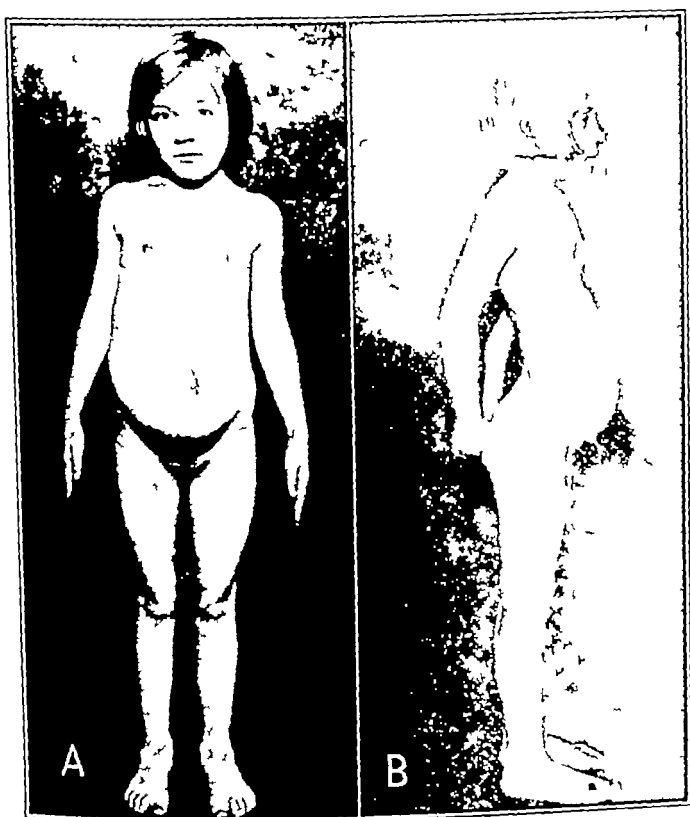


Fig 1—A, front view of the child before operation. Note the position of the umbilicus and the bulging of the right flank. B, lateral view. Note the well marked Harrison's groove.

There were no other positive physical findings of note. After making pyelograms and roentgen studies of the gastrointestinal tract (fig 2), Dr W. E. Anspach, the roentgenologist, summarized his data as follows:

- 1 A tumor mass 84 by 74 cm was present in the right upper quadrant, having a fairly dense calcified material in its wall. It was not intimately associated with the colon. It was probably a calcified cyst.
- 2 There was no evidence of spina bifida.

3 There was slight dilatation of the renal pelvis, the calices and the ureters on both sides, somewhat more on the right than on the left. There was poor concentration of dye in the bladder.

*Laboratory Studies*—The following values were obtained: hemoglobin (Sahli), 90 per cent, red blood cells, 4,300,000 per cubic millimeter, white blood cells, 10,000 per cubic millimeter, polymorphonuclears, 48 per cent, lymphocytes, 48 per cent, and eosinophils, 4 per cent. Repeated urinalyses revealed only an occasional leukocyte and epithelial cell. The Wassermann reaction was negative.

The preoperative diagnoses on November 2 were: (1) Congenital hypoplasia of the ventral abdominal musculature, (2) congenital calcified cystic abdominal tumor (gallbladder? teratoma?), and (3) mild right hydronephrosis (pressure from tumor mass).



Fig 2—A, anteroposterior roentgenogram of the tumor mass, showing its relation to the colon. B, lateral view, showing the relation of the tumor to the spine.

*Operation*—On November 2 the abdomen was opened through a right upper rectus incision with the child under ethylene and ether anesthesia. The abdominal wall was abnormally relaxed, and the right rectus muscle was very thin and markedly diminished in size. When the abdominal cavity was entered, an aneurysm-like mass about 10 cm in diameter was found lying just underneath the liver (fig 3) and to the right of the gallbladder, which was pendulous, elongated and distended with bile, measuring approximately 14 cm in length. The mass, which was attached to the relaxed round ligament of the liver by a thin, tough, fibrous pedicle, was rough and wrinkled, having the consistency of a hard rubber ball. It was covered with many dilated and tortuous veins. After the pedicle had been ligated with chromic catgut, the tumor mass was removed in toto, and the abdomen was closed in the usual manner, without drainage. The child's condition was good at the end of the operation.



Her postoperative course was uneventful, and renal functional tests revealed no abnormality. She was discharged home in good condition on November 18. When last seen in the outpatient department, on Nov. 16, 1938, the child seemed to be entirely well and without symptoms, although the abdomen was still swelling and required support.

*Gross Description of Tumor Mass*—The specimen weighed 235 Gm., was oval and measured 8.5 cm. in its largest diameter and 7 cm. in width. The anterior, or presenting, surface (fig. 4 A) was thrown into a rich convoluted pattern, greatly resembling in this respect the surface of a normal brain, or a "Parisian coiffure." The posterior surface, or under surface, tended to be smooth. Transversing it were several flattened, tortuous vessels which evidently entered into the formation of the vascular stalk by which the mass was suspended beneath the liver. When sectioned (fig. 4 B) the mass was seen to be composed of three distinct layers. The outer layer, of thick wavy folds, determined its external appearance. It was of fleshlike consistency, was pink to gray and measured 0.5 to 1 cm. in depth. On cross section this stratum consisted of fairly dense pink

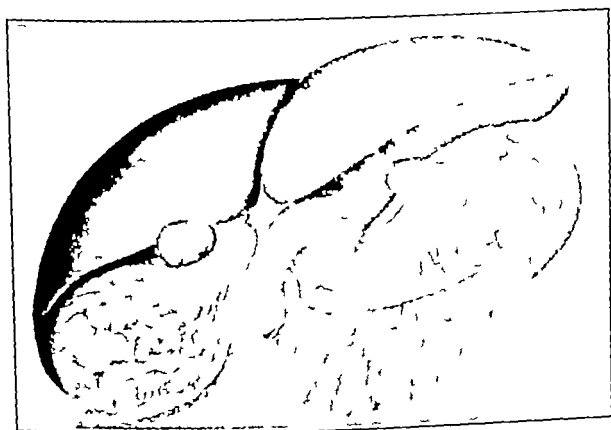


Fig. 3—Photograph of artist's drawing showing the position and appearance of the cyst at the time of operation. Note the pedicle.

connective tissue covered over by a thin, shiny capsule closely adherent to the fluted rolls and dips. In places a fine red stippling suggested the presence of blood vessels that had been transected.

A distinct cleavage plane separated it from the middle layer, which was responsible for the gross shape and outline. This was a dense, white, fairly rigid calcified shell about 2 mm. in thickness. It resembled a fetal skull in appearance and resiliency. From its inner surface, around the entire circumference and filling the largest part of the enclosed space, there projected a fine friable, coral-like, papilliferous light brown growth. Its exquisite design suggested that it was composed of some type of delicate organized tissue. An aqueous medium of about 30 cm. of dark brown cloudy fluid filled its interstices and occupied the core. This fluid had a positive benzidine reaction for blood and contained no recognizable cytologic elements. The lining vaguely resembled marine flora. At one end of the bisected mass a tough fibrous partition passing across from side to side divided the mass into two unequal portions. The larger one conformed to the foregoing description. The small compartment like a magnified

operculum of a trematode ovum (fig 5), contained a denser yet more friable homogeneous material of identical color and without recognizable structure. The tumor mass was less dense than water.

*Microscopic Description (Hematoxylin and Eosin, Mallory's Aniline Blue and Verhoeff's Elastic Tissue Stains)*—The wall of the cyst was made up of three distinct layers, the outer of which was composed of loose fibrous tissue containing

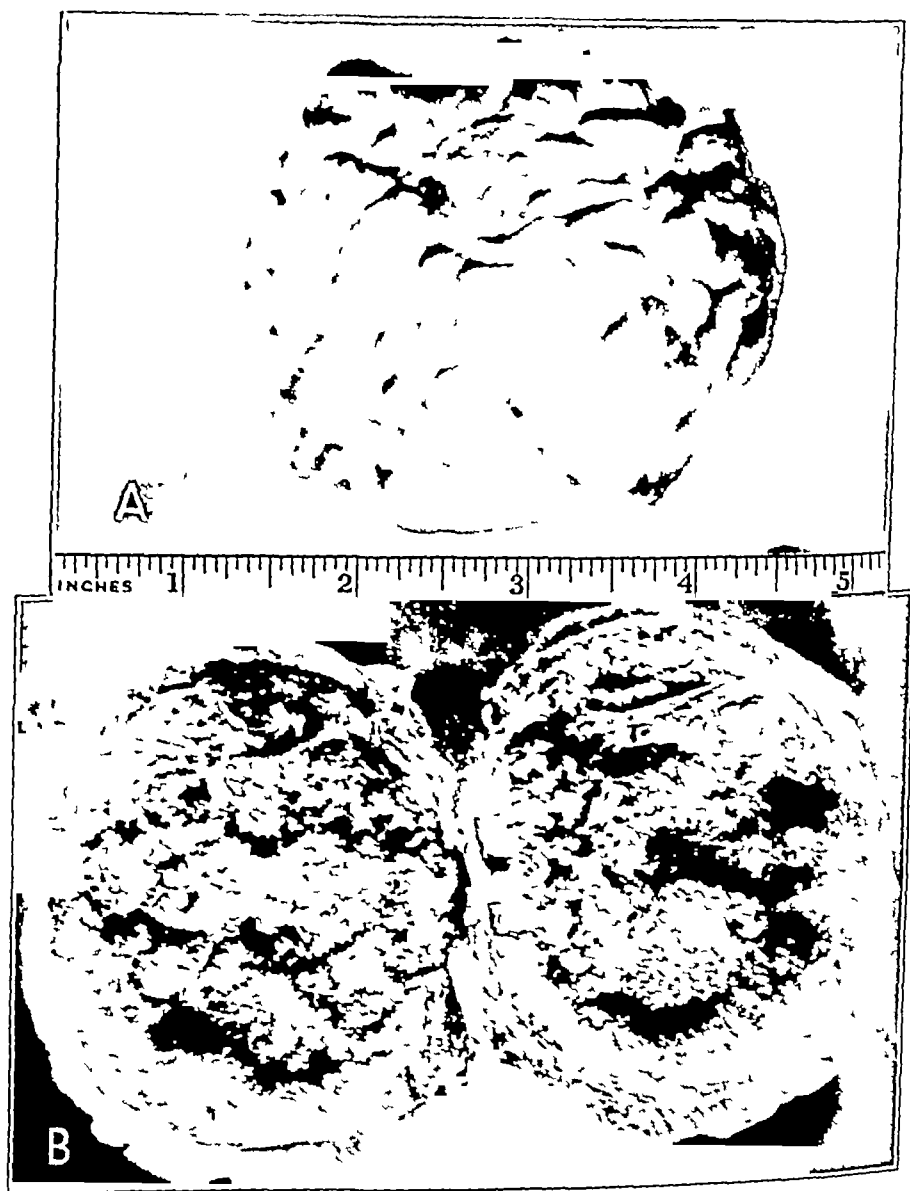


Fig 4—A, external surface of the cyst, showing its resemblance to a fetal brain or a "Parisian coiffure." B, bisected cyst, revealing its three distinct layers. Note the inner calcified layer.

many large and small dilated engorged blood vessels, mainly veins which varied from 2 to 5 mm in thickness. In focal places small clumps of irregularly arranged regions of liver cells (fig 6) were seen. No other tissue was recognizable, and there was no increase in the elastic fibers. The outermost layer of tissue was thin and fibrous.

The middle layer was composed entirely of homogeneous, dense calcified material having an average thickness of 1 mm. It was not intimately bound to either the outer or the inner layer. In a few places blood vessels were enclosed in its structure.

The innermost layer was composed of a somewhat uniformly dense, homogeneous material which stained poorly. Here and there were clumps of partially disintegrated cells which could not be identified but resembled an old blood clot.

The final diagnosis was calcified pedunculated cyst of the liver.

CASE 2—M. T., a white girl aged 6 months, was brought to the Children's Memorial Hospital on Sept. 6, 1933 by her mother, who had noticed for several months that the child's abdomen had become abnormally large. In every other way the child had been healthy and normal since birth.

*Physical Examination*—The baby appeared bright and active and, except for the abdomen, seemed to be of normal development. Examination of the head,



Fig. 5—Roentgenogram of the surgically removed tumor. Note the resemblance to a trematode ovum.

neck and extremities revealed no abnormality. The abdomen was tremendously enlarged. The greatest circumference, which was 5 cm. above the umbilicus, was 53 cm. while the thoracic circumference at the level of the nipples was only 38 cm. The superficial veins were prominent on the abdominal wall and the skin was tense and shiny. Palpation disclosed a cystlike mass on the right extending from the costal margin down to Poupart's ligament and medially to the midline. It did not seem to be movable in any direction. On percussion the mass sounded dull, while the rest of the abdomen was very tympanitic. There was no tenderness over the tumor mass or elsewhere. The chest appeared to be shortened longitudinally, with some flaring of the lower ribs. The distance from the apex to the ninth rib was 4 inches (10 cm.). The breath sounds were uppe ed over the base of the lung. The heart was evidently displaced to the left as the right border was to the right of the sternum and the apex beat was 5 cm. to the left of the nipple line.

Roentgenograms made after intravenous injection of a dye showed nothing abnormal in the urinary tract

The preoperative diagnosis was omental or mesenteric cyst

*Operation*—On September 9, with the child under ether anesthesia, the abdomen was opened by an upper right rectus incision. This disclosed a large, thick-walled cyst attached to the under surface of the liver but not adherent to any other abdominal viscera. After aspiration of  $1\frac{1}{2}$  liters of greenish fluid it was evident that the cyst could not be completely removed, because its superior surface formed the inferior capsule of the liver. A large part of the cyst was

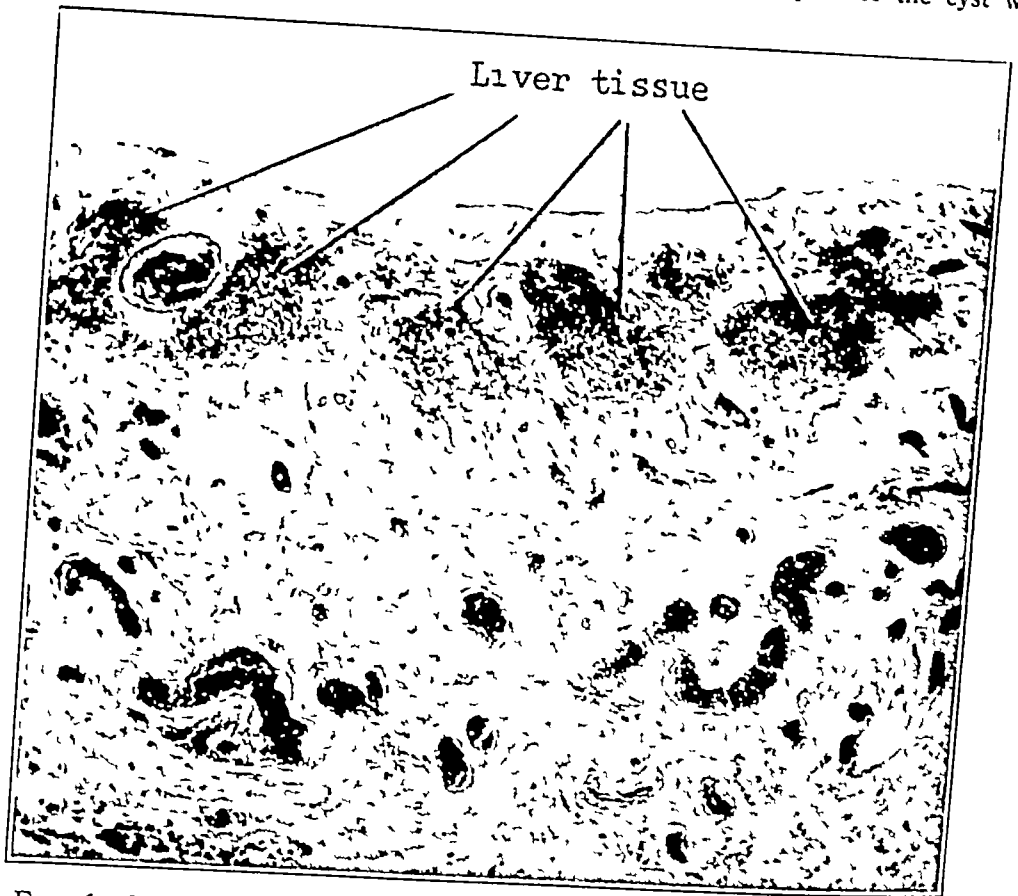


Fig 6—Photomicrograph (hematoxylin and eosin,  $\times 30$ ) showing clumps of liver cells in the outer layer of the cyst

removed, and the remainder was marsupialized to the peritoneum of the abdominal wall. The cyst cavity was packed with iodoform gauze and the abdominal wound closed about it.

The cyst fluid on examination showed a cell count of 4,230, a specific gravity of 1.010 and no evidence of bile.

*Subsequent History*—The abdominal wound healed kindly, and for several months the cyst cavity was packed repeatedly with iodoform gauze. As films taken of the cyst after injection of iodized poppyseed oil showed little reduction in the size of the cavity and it was becoming very difficult to insert the gauze packing, various sclerosing substances, such as tincture of iodine and silver nitrate solutions, were applied to the lining of the cyst, without any appreciable

effect Two years after the first operation another exploration of the abdomen was made through the scar of the first operation The cyst cavity was found to be much reduced in size but still irremovable from the under surface of the liver The cavity was swabbed with phenol and alcohol, and marsupialization was reestablished. Profuse drainage from the cyst went on as before

As roentgenograms made in August 1937 after injection of iodized poppyseed oil showed little diminution of the cyst, a sufficient quantity of Zenker's solution was injected to fill the cavity At first this caused abdominal discomfort for several hours, but after weekly injections the pain gradually lessened. The amount of Zenker's solution that could be injected slowly decreased until September 1939, when the sinus closed. It has remained closed to the present date



Fig 7—Photomicrograph (Mallory's aniline blue stain,  $\times 30$ ) showing the outermost layer of the cyst, with loose connective tissue and many engorged blood vessels

*Microscopic Description*—The cyst wall consisted essentially of three layers (fig 8) The inner layer was the lining epithelium the middle layer consisted of loose connective tissue and the outer layer of liver tissue

The inner lining of the cyst was formed by a well preserved layer of stratified epithelium (fig 9) The basal cells of this epithelium were polyhedral with their nuclei arranged at right angles to the surface The more superficial cells were elongated, flattened in a direction parallel to the surface The epithelial layer was three to five cells deep with nuclei which were in many respects similar to those of the liver or bile duct cells The superficial cells had undergone moderate

degenerative changes. The basement membrane of the epithelium was not distinct, but there was no proliferation of epithelial elements into the cyst wall.

The next layer of the cyst wall was formed by more or less cellular collagenous fibrous tissue. The fibers and cells were arranged parallel to the surface. In a few areas there was proliferation of young fibroblasts. Here and there loose foci of polymorphonuclear leukocytes, eosinophils and lymphocytes were encountered. Moderate numbers of small blood vessels were present in this layer. In an outward direction there was a gradual transition into a loose connective tissue, in which numerous fairly large blood vessels and endothelium-lined lymphatic channels were observed. A narrow capsule-like strip of dense fibrous tissue

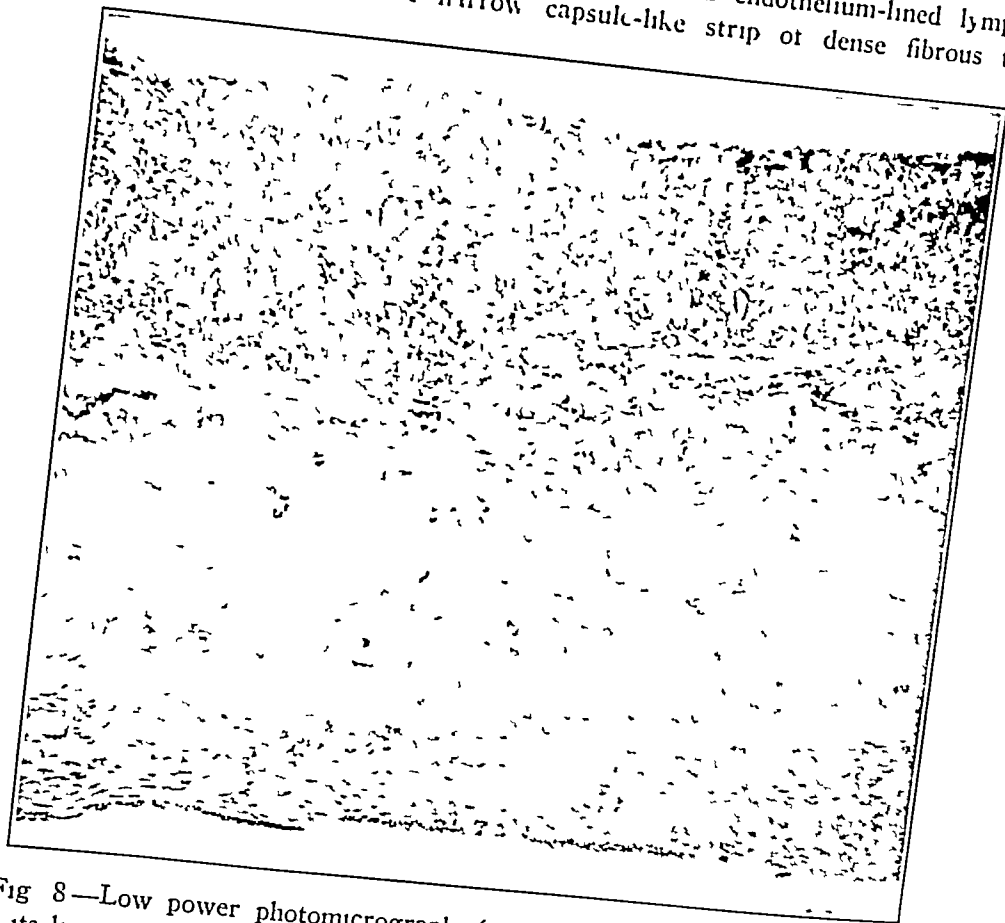


Fig 8—Low power photomicrograph ( $\times 35$ ) of the entire wall of the cyst with its lining epithelium. The middle portion consists of loose connective tissue, the outer portion, of liver tissue and its capsule.

separated this layer of vessels and lymphatics from a bandlike zone of liver tissue (fig 10). The liver cells were typical as regards size, shape, staining properties and the character of the nuclei. The cytoplasm was somewhat pale, and the cell borders were distinct. The cells were arranged in parallel cords at right angles to the surface. The sinusoids were, as a rule, compressed, but here and there empty endothelium-lined channels were observed between the cords of liver cells.

Along the inner border of the liver tissue bile ducts were observed at fairly regular intervals. These were lined with columnar epithelium and were sometimes mildly dilated but always empty. The layer in which the bile ducts were

seen was mildly infiltrated with lymphocytes, eosinophils and polymorphonuclear leukocytes. Toward the periphery, somewhat distended venules, clearly corresponding to central veins, were seen between the rows of liver cells. The outermost layer of the cyst was formed by a thin, compact layer of collagenous fibrous tissue, which corresponded to the liver capsule and was lined with flat endothelial cells.

The final diagnosis was nonparasitic cyst of the liver.

#### GENERAL CONSIDERATIONS

Solitary nonparasitic cysts of the liver occur at all ages from fetal to late adult life<sup>2</sup> but are found rarely in infants and young children.



Fig 9—Photomicrograph ( $\times 640$ ) The cyst is lined by stratified epithelium the surface cells of which have been altered by the pressure of the contents of the cyst.

Multiple cysts may occur in the liver alone but are most often associated with cystic disease of other organs or with congenital malformations. Cysts seem to occur more often in females than in males the ratio being 4:1. This is explained on the basis that developmental defects are well known to be more common in the former sex.

Most cysts are located in the anteromedial portions of the right lobe of the liver, but the left and quadrate lobes may be involved. In

a few cases the central part of the liver was the site of the cyst. The round ligament was involved in a few cases described by Harrington,<sup>3</sup> as it was in 1 of my cases (fig 3). The amount of liver tissue displaced by these cysts is variable, sometimes the entire lobe is destroyed. Some cysts are microscopic, while others may fill almost the entire abdomen. Cysts of the liver grow very slowly if at all, and this in most cases accounts for the lack of signs and symptoms, as the adjacent organs adapt themselves to the presence of the tumor mass. Many



Fig 10—Photomicrograph ( $\times 80$ ) The peripheral portion of the cyst is covered by the capsule of the liver, beneath which there is well formed liver tissue.

of the large cysts are pedunculated and may show a marked degree of motility, as in my first case. When the pedicle is long, strangulation and hemorrhage may occur, and these two complications usually account for acute symptoms. Another characteristic of nonparasitic cysts is the low internal tension, the reverse being true of hydatid cysts, as has been recorded by Italian writers.

<sup>3</sup> Harrington, S. W. *S. Clin. North America* 6:1191, 1926.



The external surface of these cysts is usually smooth, glistening and grayish blue, often showing many dilated veins and bands of tough fibrous tissue. The internal surface may be less regular and smooth, and the thickness of the wall is extremely variable. The contents of the cyst vary from a clear, watery, sometimes yellowish brown fluid, neutral or alkaline in reaction, to a semisolid material resembling an organizing blood clot. An analysis may show albumin, mucin, cholesterol, blood, hematin, hemosiderin, tyrosin, some granular and cellular debris and, rarely, bile. Some writers claim that the older cysts contain no bile because it is being constantly absorbed.

The microscopic appearance of the cyst wall usually demonstrates that it consists of three fairly distinct layers, an inner layer of loose tissue rich in ill defined cellular debris, a circular dense middle layer, poor in cell nuclei, containing a few blood vessels with thickened intima, and a loose outer layer rich in blood vessels, elastic fibers, muscle fibers, clumps of bile ducts and liver cells, covered with a thin fibrous capsule.

Various classifications of nonparasitic cysts of the liver have been attempted, but Sonntag's<sup>4</sup> is the one generally accepted: (1) blood cysts and degenerated cysts, (2) dermoid cysts, (3) lymphatic cysts due to obstruction or congenital dilatation of the lymphatics, (4) endothelial cysts, (5) cysts due to obstruction of bile ducts and (6) proliferative cysts (cystadenomas).

The possible mode of origin of these cysts has been discussed in detail by Bland-Sutton,<sup>2</sup> Moschcowitz,<sup>5</sup> Kaufmann<sup>6</sup> and Ewing.<sup>7</sup>

From all the theories expressed one must conclude that nonparasitic cysts of the liver are congenital and are of biliary origin, perhaps arising from aberrant bile ducts which result in benign cystic adenomas.

Solitary nonparasitic cysts of the liver<sup>8</sup> are usually symptomless unless they become large enough to give pressure symptoms or are palpable. It has been stated<sup>1b</sup> that in most cases symptoms are not produced in childhood other than the presence of an abdominal mass.

4 Sonntag, E. *Beitr z klin Chir* **86** 327, 1913.

5 Moschcowitz, E. *Am J M Sc.* **131** 674 1906.

6 Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie* ed 6 Berlin, G. Reimer, 1911, vol 1 p 608.

7 Ewing, J. *Neoplastic Diseases* ed 3 Philadelphia W B Saunders Company, 1928, p 731.

8 Witzel O. *Centralbl f Gynäk* **4** 561 1880. Sanger M and Klepp A. *Arch f Gynäk* **16** 415, 1880. Miller G B. *Am J Obst* **18** 182 1903. Shaw H L K and Elting A W. *Arch. Pediat* **26** 818 1909. Lowenburg, H. *ibid* **35** 285, 1918. Everidge J. *Lancet* **1** 1748 1914. Alexander C R. *Edinburgh M J* **32** 61, 1925. Scalone I. *Policlinico (sez chir)* **31** 200 1927. Elrison E L. *Ann Surg* **99** 691 1934. White M. *Arch Dis Child* **11** 319, 1936. Bagot, W S. *Dublin J M Sc* **93** 265 1892. Ricketts H D and Kantback A A. *Virchows Arch t path Anat* **130** 488 1892.

in the right upper quadrant. When symptoms occur they are usually nausea, vomiting, diarrhea, pain in the upper part of the abdomen and, rarely, jaundice. The correct diagnosis of such cysts of the liver is difficult, being made only at operation or at autopsy. Roentgen examination of the abdomen may show the tumor to be a part of the liver shadow, and Hofmann (cited by Stoesser and Wangenstein<sup>1a</sup>) brought out the differential points of such an examination. It was suspected in my first case that the tumor was attached to or associated with the gallbladder. With large pedunculated cysts the motility may be in all directions, the downward motion, however, being limited by the attachment to the liver. Pneumoperitoneum as a diagnostic aid has been disappointing, but direct visualization of the tumor with the peritoneoscope may be of diagnostic help.

Surgical removal as done in my first case is the treatment of choice when possible. Complete extirpation cannot always be done, however, and drainage and marsupialization as done in my second case may be the procedure of necessity. Fatalities have been reported due to shock from the sudden release of intra-abdominal pressure. This can be avoided by the injection of epinephrine hydrochloride subcutaneously before the cyst is opened and by slow removal of the fluid. This may also prevent complete evisceration, which has been observed by some surgeons, especially in treating these cysts in children. The prognosis in general is good if the patient survives operation, but the operative mortality of nonparasitic cystic disease of the liver in the reported cases varies between 10 and 30 per cent.

#### COMMENT

From the description of my 2 cases it is quite evident that both cysts were congenital. In case 1 the tumor was present at birth and was associated with congenital weakness and atrophy of some of the muscles of the abdominal wall, and in case 2 it was discovered a few months after birth.

As liver tissue was observed in the walls of both cysts, it is fair to assume from that fact and from their location that the cysts originated in connection with the liver. The first case is unique in its bizarre roentgen and gross appearance. A review of the literature fails to show a similar case. Because liver cells were observed in the outer layer of the cyst, I believe that this tumor mass was originally an accessory lobe of the liver and that during the intrauterine period, when the abdominal contents were returned to the abdomen and rotating to assume their normal position, this mass of liver tissue became twisted on its pedicle, producing necrosis of its central portion from loss of blood supply. This was followed by the deposition of calcium in its middle portion. Subsequently the tumor mass failed to increase in size.

owing to faulty blood supply and failed to give symptoms because of its location and attachment. In short, I believe that this was a congenital nonparasitic calcified cyst of an accessory lobe of the liver.

In the second case the presence of compressed liver cells in the lining of the cysts would seem to indicate that the cyst arose from obstruction of the biliary ducts near the inferior capsule of the liver, producing a cystadenoma of the liver.

#### CONCLUSION

Two congenital nonparasitic cysts of the liver in children are presented. In 1 case the calcification and bizarre appearance of the cyst are pointed out. The use of Zenker's solution as a sclerosing agent in the obliteration of these cysts is suggested.

Dr W Price Killingsworth, of Port Arthur, Texas, assisted in describing the pathologic specimens.

122 South Michigan Avenue

# CHANGES IN BONES AND JOINTS RESULTING FROM INTERRUPTION OF CIRCULATION

## I GENERAL CONSIDERATIONS AND CHANGES RESULTING FROM INJURIES

DALLAS B. PHEMISTER, M.D.

CHICAGO

Lesions of various organs resulting from interruption of the circulation are of common occurrence, and their pathologic and clinical aspects are generally known to the members of the medical profession. Examples are occlusions of the coronary, cerebral and pulmonary arteries and infarctions of the kidney and of the spleen. However, in the case of bones the same generalizations cannot be made. Although it has been accepted since the report of Langer<sup>1</sup> in 1875 that the bones contain end arteries, knowledge of changes in bones and joints from vascular blockage was slow in developing. There are a number of reasons for this: first, the absence or mildness of immediate symptoms resulting from simple interruption of circulation in bone, second, postmortem examinations of the skeleton are much less common and less extensive than are those of the viscera, third, operation affording a chance for pathologic examination is seldom indicated with most forms of aseptic bone necrosis, and fourth, certain roentgen signs of this condition which are late in appearing were long confused with those of other chronic lesions.

Septic embolism of bones has long been regarded as one of the causes of pyogenic and tuberculous osteomyelitis, but definite information on this point is scanty. Volkmann<sup>2</sup> in 1864 reported multiple suppurating infarcts of bones in a case of septic endocarditis in which necropsy was performed. There is a difference of opinion as to the role of vascular blockage in the pathogenesis of the usual hematogenous osteomyelitis, whether it arises from the activity of bacteria which lodge in the tissues and sinusoids of the bone or from that of organisms contained in small emboli which block end arterioles of the metaphysal

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From the Department of Surgery of the University of Chicago

1 von Langer, C. Ueber das Gefäss-system der Rohrenknochen, mit Beiträgen zur Kenntnis des Baues und der Entwicklung des Knochengewebes, Vienna, K. Gerolds Sohn, 1875

2 Volkmann, R. Embolische Knochennekrose nach Endocarditis, Arch f klin Chir 5 330, 1864

regions Information is difficult to obtain because in either case the initial lesion is small and is rapidly obscured by spread of the inflammation to surrounding tissues That a large artery may be blocked by a septic embolus resulting in massive bone necrosis with slow secondary infection and resolution of the necrotic area has been claimed by Axhausen Such an occurrence would necessitate the existence of a septic focus in the pulmonary veins, the left side of the heart or the arteries, giving rise to the embolus, as particles passing through the lungs would be too small to produce the obstruction König<sup>3</sup> expressed the belief which has been extensively accepted, that areas of necrosis associated with tuberculosis of the metaphyses and epiphyses, some of which are wedge shaped, are the result of embolism of caseous tuberculous material gaining entrance to the arterial circulation from tuberculous lungs by way of the pulmonary veins While the theory is very plausible, direct proof is still lacking

Knowledge of simple or aseptic interruption of the circulation in bone has been developed mainly during the past thirty years, owing in large part to the contributions of Axhausen, who, together with Bergmann,<sup>4</sup> has recently published a very comprehensive review and extensive bibliography of the subject However, since then there have been other reports which have added considerably to knowledge of the subject

The first information on the effect of aseptic interruption of the circulation in bone was obtained by a study of transplanted bone Ollier expressed the opinion that the entire transplant remains alive, becomes attached to the bone and subsequently undergoes more or less transformation in adjusting to its location and function Barth<sup>5</sup> was the first to recognize that the bone tissue dies and later is invaded and replaced by new bone He expressed the opinion that there is death of the entire transplant and that new bone grows into it from the bone into which it was transplanted Axhausen first demonstrated that the periosteum and endosteum of the transplant survive and take the most active part in generating new bone which replaces the dead bone<sup>4</sup> But in case the transplant is extensively and snugly embedded in bone the invasion and replacement may be in large part by tissue from the surrounding bone Cornil and Coudray<sup>6</sup> demonstrated that with frac-

3 König F Die spezielle Tuberculose der Knochen und Gelenke Berlin August Hirschwald 1896

4 Axhausen, G, and Bergmann E Die Ernährungsunterbrechungen im Knochen in Henke F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie Berlin, Julius Springer 1937 vol 9 pt 3

5 Barth Ueber histologische Befunde nach Knochenimplantation Arch f klin. Chir 46 409, 1893

6 Cornil and Coudray Du cal au point de vue experimental et histologique J de l'anat et physiol 50 103 1904

tures in rabbits there is necrosis of the cortex for a short distance back from the fracture line, with subsequent creeping replacement of the dead bone by new bone. Lexer<sup>7</sup> performed homotransplantations of joints, with the result that after successful union and transformation of the bone the articulation gradually broke down, with marked impairment of function.

Aseptic necrosis developing in bone that has not been transplanted was recognized first in lesions of the epiphyses and short bones both in children and in adults. Lesions situated in the shaft have only recently been recognized. The epiphysial disturbances designated as Legg-Perthes disease, Kohler's disease of the metatarsal bone, Osgood-Schlatter disease and Kienbock's lunatum and Kohler's tarsal navicular diseases were gradually identified by pathologic examinations as necrosing lesions. It was learned simultaneously that certain fractures bordering on joints and dislocations may cut off blood supply and cause necrosis of the end of the bone. Axhausen observed a case in which rather recent anemic infarcts of the bones of an adult were present, some of which were in the epiphyses and others in the metaphyses, which he considered due to embolism. Kahlstrom, Burton and I<sup>8</sup> were the first to report cases of very extensive aseptic necrosis of both shafts and epiphyses of bones terminating in permanent large calcified infarcts in the shafts and in arthritis deformans wherever the necrosis bordered on a joint.

Pathologic and roentgen studies have revealed certain reactions of the surrounding living bone and joint structures to necrotic bone and necrotic cartilage resulting from aseptic interruption of the circulation. A reparative reaction is set up in the living bone about the dead area which bears some resemblance to fibrous callus formation in fracture healing. But removal of dead bone as well as formation of new bone must be accomplished in the process of repair. A zone of fibrous tissue forms in the marrow spaces of spongy bone or along the surface of compact bone about the necrotic focus. This fibrous tissue gradually invades the marrow spaces of the dead cancellous bone, breaking down and replacing the dead marrow. As the fibrous zone advances into the dead bone on the one side it becomes transformed into an advancing osteogenetic zone on the other. In this zone the fibrous tissue (i. e.,

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7 Lexer, E. *Die freien Transplantationen*, Stuttgart, Ferdinand Enke, 1924, pt. 2.

8 Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. *Aseptic Necrosis of Bone*. I. Infarction of Bones in Caisson Disease Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, *Surg., Gynec. & Obst.* 68: 129, 1939, II. Infarction of Bones of Undetermined Etiology Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, *ibid.* 68: 631, 1939.

fibrous marrow) is transformed into bone, which is laid down on and gradually replaces the old dead bone, and into hemopoietic and fatty marrow. The dead bone is removed in part by osteoclasts and in part by the direct action of the new bone as it is being laid down, a process which has been called "creeping substitution." Necrotic cortex is invaded and replaced as in a transplant. These two processes of fibrous invasion and of metaplasia and replacement of the dead bone by new bone usually go hand in hand in a relatively narrow band (fig 22). But in some cases the fibrous invasion may be far in advance of the zone of transformation, leaving a thick zone of dead bone filled with fibrous marrow. There is considerable variation in the rate of progress of the transformation and in the extent to which the dead bone is removed and replaced by new bone. These factors are influenced by age, size and location of the necrotic area, function, trauma and non-union of fractures which may be present. Aseptic necrotic bone in children as in Legg-Perthes disease is nearly always completely replaced by new bone, and substitution proceeds more rapidly than in adults. Small necrotic areas continuous with living bone are usually completely replaced by new bone in the course of a few weeks or months. But the presence of an ununited fracture may greatly delay invasion and transformation, as in case 3.

Until recently it was the generally accepted view that the reparative impulse would last as long as dead bone persisted and that the necrotic area, regardless of size, was eventually all invaded and replaced by new bone. But the reports by Kahlstrom, Burton and me<sup>8</sup> and by me alone<sup>9</sup> have shown that in the case of adults large necrotic areas, especially in the shafts of bones but also in the head and condyles of the femur, may be incompletely removed. A possible factor in explanation of this may be that after a considerable part of the peripheral portion has been replaced the strength of the bone becomes sufficient for the function which it is called on to perform. The reparative stimulus is then greatly reduced or removed, the necrotic area remains stationary in size, and the fibrous zone of transformation about it may undergo more or less extensive calcification and ossification. There may also be calcification scattered throughout the necrotic portion inside the fibrous zone. These features are illustrated in femoral heads by figure 22 and in the shafts in the report by Kahlstrom, Burton and me.

Function hastens to some extent the rate and increases the extent of repair. It should, however, be limited well within the strength of the necrotic bone and of the newly forming bone during the major part of the period of creeping substitution. If in case of necrosis of the

9 Phemister D B Aseptische Knochennekrose bei Frakturen, Transplantationen und Gefässverschlüssen, *Ztschr f orthop Chir* 55 161 1931

ends of the bones there is too much weight bearing, strain or trauma in any form, there will be fracture of the necrotic bone or of the weak new bone along the zone of substitution, with more or less collapse of the articular portion, erosion of the necrotic trabeculae from friction of fragments and, in some cases, the establishment of fibrous or fibro-cartilaginous union or even of pseudarthrosis between the necrotic and the living portions. This is illustrated by case 9 (figs 13 to 16). The bone meal created by the erosion may be driven into the cancellous spaces of the dead portion to some extent. The establishment of a line of nonunion may greatly retard invasion and replacement of the dead bone and increase the deformity of the joint (case 6). When there is necrosis of bone bordering on a joint there is always more or less secondary change in the articulation.

If there is collapse of the bone the articular cartilage is damaged. The nutrition of the cartilage is derived partly from the synovial fluid and partly from tissue fluid coming from the circulation of the underlying bone. During the period of growth the cartilage may get adequate nutrition from the synovial fluid alone and continue to grow, as is shown by the experiments of Nussbaum<sup>10</sup> in which the blood supply of the bone of the epiphysis was severed. Also, pathologic studies of the necrosing lesions of the epiphyses during the period of growth have shown that, while the cartilage may show evidences of nutritional disturbance in places, it in large part remains alive, becomes thicker than normal as in Legg-Perthes disease and after the necrotic bone is replaced takes part in further epiphysal growth.

However, in adults the articular cartilage is less dependent on synovial fluid for nutrition. This is perhaps related to the more fibrous and less penetrable character of the layer along its free surface. Consequently, interruption of the circulation in the bone of the epiphysis causes interference with the nutrition of the cartilage. This varies considerably in degree with the case. Usually it is quite obvious, and the cartilage cells, especially "deep in," gradually diminish in staining power. A striking fact is that if for a variable period (up to several months) there is invasion and creeping replacement of the underlying cortex by new bone, the new blood supply underneath the cartilage furnishes it with nutrition, and its cells largely regain their normal staining properties. Figuratively speaking, the cartilage is rescued from a state of hibernation during which it received only scant nutrition from the synovial fluid. This is illustrated by case 8 (figs 24 and 25). One patient examined ten weeks and another examined twenty-two weeks after fracture of the

10 Nussbaum. Die arteriellen Gefäße der Epiphysen des Oberschenkels und ihre Beziehungen zu normalen und pathologischen Vorgängen, Beitr z klin Chir 130 495, 1923



neck of the femur with necrosis of the femoral head showed complete restoration of staining properties of the cartilage in the regions where underlying living bone had been restored, while that over the remaining dead area stained feebly. If, however, the replacement of the underlying bone by new bone is delayed for longer than nine to twelve months the cartilage is apt to die. Dead cartilage may remain for long periods, may be eroded in weight-bearing portions or may be replaced by fibrocartilage or even by bone if the underlying living bone is eventually restored.

In cases of long-standing involvement a chronic deforming arthritis is usually established, consisting of fibrillation and faulting of the fibrocartilage, marginal lipping, villous arthritis, osteocartilaginous loose bodies and, in cases of advanced involvement, disintegration and deformity of the articulation. The most important known factor in the production of the arthritis deformans is the necrotic articular cartilage, although eroded pieces of bone have been found at the center of the cartilaginous loose bodies in some cases. Axhausen<sup>11</sup> found that when cartilage of the knee joint of the dog was killed *in situ* by chemicals, heat or a high frequency electric current, the changes of arthritis deformans developed, involving the articular cartilage, the ends of the bone and the synovial lining. These changes are illustrated in case 10 and in the cases reported by Kahlstrom, Burton and me.

Roentgen studies have come to play an increasingly greater role in the recognition of the effects of circulatory blockage of the skeleton as they have been correlated with the pathologic observations in the bones and joints. Changes in density of the bone result from atrophy of disuse, from creeping replacement of dead bone by new bone, from pathologic fractures and collapse of the dead bone bordering on joints, from compression of dead trabeculae, from infiltration of bone sand into the dead marrow spaces and from calcification of the line of demarcation and the interior of old stationary necrotic areas located in the medullary and cancellous regions. In the case of joints they occur from calcification of cartilaginous loose bodies, marginal lipping, loss of articular cartilage and subchondral sclerosis in the later stages of arthritis deformans. Since time is required for the development of all of these changes, there are no demonstrable roentgen changes in the early stages of aseptic necrosis. In case the cause of necrosis is a fracture followed by nonunion resulting in marked disuse, there is enough atrophy of the adjacent living bone in one to two months to cause it to cast in roentgenograms a shadow fainter than that cast by the dead bone, which retains its original density. Fibrous tissue invasion of the dead bone causes no change in density, but creeping substitution by new bone alters density. If it takes place

11 Axhausen, G. Neue Untersuchungen über die Rolle der Knorpelnecrose in der Pathogenese der Arthritis, *Arch f klin Chir* 104 20 1914

in the presence of a considerable degree of disuse, as in a necrotic femoral head in a case of ununited fracture of the neck of the femur (case 8, fig 24), the new bone is less dense than the old and casts a fainter shadow. In some of these cases central portions of the head may be replaced by fatty bone marrow, which gives the roentgen appearance of a cavity. It, however, there is little or no disuse, the new bone is laid down in greater amounts, and the density approximates the normal. But the shadows of the trabeculae are usually irregular, which may suggest the previous existence of a necrotic area. Flattening of the articular surface and fracture lines within or at the limits of the dense bone are important signs. Compression of trabeculae, especially in necrosing lesions in children, may give rise to some degree of increased density. Axhausen and Bergmann<sup>4</sup> have reported that the broken-down bone of a collapsed region may be so finely powdered that it works its way under pressure into the cancellous spaces of the remaining dead bone, causing it to cast shadows of increased density in roentgenograms. Weil, on the other hand, concluded that the amorphous material filling these cancellous spaces is disintegrated blood.<sup>4</sup> Examination of materials available for this report showed only relatively small amounts of eroded bone dust driven into the marrow spaces of the dead bone, probably not enough to increase materially its density in roentgenograms. Material resembling that shown in Axhausen's photomicrographs was seen, but it appeared to be mainly the debris of necrotic marrow and blood, as in figures 15*A* and 16*A*, with relatively slight infiltration of the dead bone by bone dust. The calcified and ossified line of demarcation which may develop about a stationary necrotic area in the cancellous bone or the medullary cavity of the shaft casts a definite shadow of increased density in roentgenograms (case 7). There may also be sufficient calcification within to cause the entire necrotic area to cast a more or less blotchy shadow of increased density, as in previously reported cases (case 8) and in others to appear in part II.

*Causes*—The causes of interruption of circulation are in general less well understood in the case of bone than in the case of soft parts. The best known cause is injury of the blood vessels produced by fractures, dislocations and operations. For this reason the lesions resulting from injury will be considered first, and those due to other and little understood causes will be left for consideration in part II.

#### CHANGES RESULTING FROM INJURIES

Traumatic interruption of the circulation of bone is most frequently caused by fracture. In fact, there is a variable amount, usually small, of necrosis of fragment ends in almost every case of fracture, but it remains unrecognized and undergoes creeping substitution with the healing of the fracture. Extensive necrosis, which may impede the repair

of the injury and be diagnosed in roentgenograms, is most often seen with comminuted fractures and with fractures of the ends of certain bones and of short bones of the carpus and tarsus. Ransohoff<sup>12</sup> reported a case of fracture of the middle third of the shaft of the humerus followed by marked wavy reduction in density of the entire lower fragment, which he interpreted as due to injury of the nutrient artery followed by necrosis and repair. Ten years later a roentgenogram showed the appearance restored to normal.

**Comminuted fractures** If the ends of the fragments are shattered, the broken-off pieces usually undergo partial to complete necrosis, but in some cases blood vessels passing by way of attached soft parts keep the circulation intact. The unossified periosteal and endosteal osteogenic elements of the splinter take part in callus formation if the splinter is not widely displaced from the fracture site. There is also invasion of the dead bone by blood vessels and osteogenic tissue, and creeping replacement of the dead bone by new bone is gradually accomplished, analogous to the changes in a transplant. If the splinter is widely displaced into soft parts it will slowly undergo absorption.<sup>9</sup> Usually the presence of necrotic bone in the splinters retards somewhat but does not greatly alter the course of healing if there are good alignment and fixation of the fracture. Lexer<sup>7</sup> and Axhausen and Bergmann<sup>4</sup> even claimed that necrotic bone at the site of fracture augments the stimulus for bony union. This is in contradiction to the general observation that the less the amount of necrotic tissue present the better any wound heals. The behavior of a large detached fragment as revealed by roentgenograms and biopsy is presented in the following case of fracture of the tibia with nonunion.

#### REPORT OF CASES

**CASE 1**—A man aged 55 fell 25 feet (7.6 meters), injuring the right leg. A roentgenogram taken immediately (fig 1A) revealed fractures of both bones of the lower third. The tibia was shattered, with a large displaced splinter and a line extending into the angle joint. At operation Steinmann pins were inserted through the os calcis and the upper end of the tibia and attached to a sterilized Roger Anderson reduction apparatus. The fracture was then cut down on, the fragments and splinter brought into good alignment, the wound closed and the extremity encased in plaster. Primary wound healing followed. The pins were removed in four weeks and the cast in fifteen weeks, at the end of which time there was motion at the site of fracture of the tibia. Roentgenograms (figs 1B and 1C) then showed bony union of the fibula and nonunion of the tibia. The upper and lower tibial fragments were reduced in density, while the splinter (x) held its original density. These findings led to a diagnosis of injury of the blood supply and aseptic necrosis of the splinter. It was probably a causative factor in the nonunion. An onlay bone grafting operation was performed one hundred

<sup>12</sup> Ransohoff, N. S. Osteoporosis of the Humerus Following Fracture. *Ann Surg* 89: 571, 1929.

and twelve days after the injury, at which time the exposed splinter was found to be pale and not to bleed from the stripped cortical surface, while the upper and lower fragments were pink and there was slight bleeding when their surfaces were denuded. Biopsy of material from the splinter was done. Only cortical grafts taken from the shaft above were applied from the upper to the lower fragments posteriorly and medially and from the upper fragment to the splinter laterally. Cancellous bone grafts were applied along the fracture lines anteriorly. Microscopic sections of the excised piece of splinter showed nearly

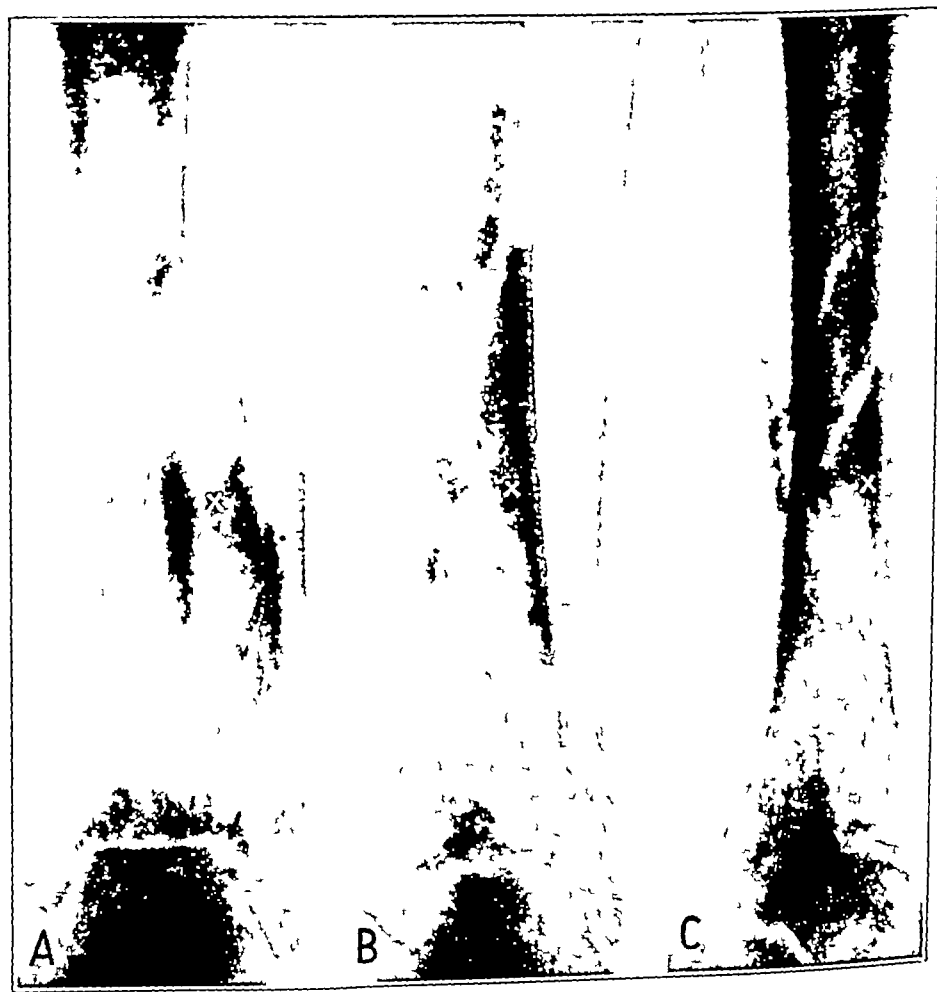


Fig 1 (case 1) —The fragment ( $\tau$ ) detached by the fracture became necrotic. *A*, fresh fracture before open reduction. *B* and *C* condition one hundred and six days later. The fracture is ununited, and the necrotic fragment ( $\tau$ ) is denser than the atrophied living fragments.

all of the lacunae devoid of cells, and where cells were present they stained poorly. There was a small amount of revascularization of canals and of creeping replacement of old cortex by new bone along the surface (fig 2). Bony union followed, but roentgenograms showed the density of the splinter remaining about the same. The patient began walking eight months after injury. Ten months after injury (fig 3, *A* and *B*) there was reduction of density in the lower portion of the splinter, indicating creeping replacement of the dead bone. Work was resumed

after about one and one-half years. Two and one-half years after the injury, roentgenograms (fig 3, *C* and *D*) showed more or less uniformity of density and wavy lamellar shadows throughout the fragments, the grafts and the splinter, indicative of complete replacement of the necrotic bone. While no roentgenograms were taken after the tenth month until after the lapse of two and one-half years, it is safe to assume from the rate of progress to the tenth month that at least two years were required for renovation of the necrotic splinter. Other cases in

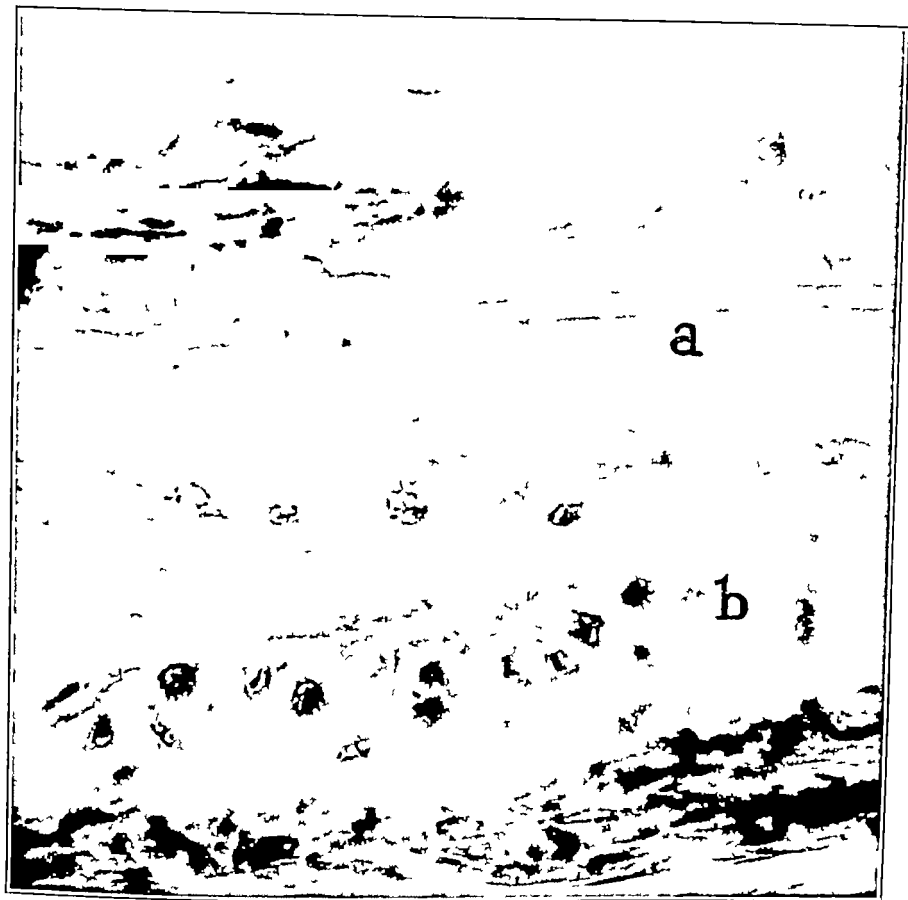


Fig 2 (case 1) —Biopsy specimen of the fragment (*r*) one hundred and twelve days after injury, showing necrotic bone (*a*) and beginning creeping replacement by new bone (*b*)

which there were large splinters but in which no biopsy was performed have been followed with roentgenograms in which similar changes in density indicated necrosis of the splinter followed by creeping replacement by new bone.

There is sometimes a good deal of aseptic necrosis to be observed on microscopic examination of the ends of fragments resected at operation for ununited fracture, especially if they are of relatively short duration.

before creeping replacement has advanced very far. The condition can scarcely be diagnosed in roentgenograms because of the frequent changes in density produced by the overlapping periosteal and endosteal callus of the fragment ends. Tear of the nutrient artery in shaft fractures may cause excessive necrosis but, if so, it rarely alters the course of the fracture. Cases of regional osteoporosis following fracture of the type reported by Ransohoff<sup>12</sup> may result from nutrient artery injury. During

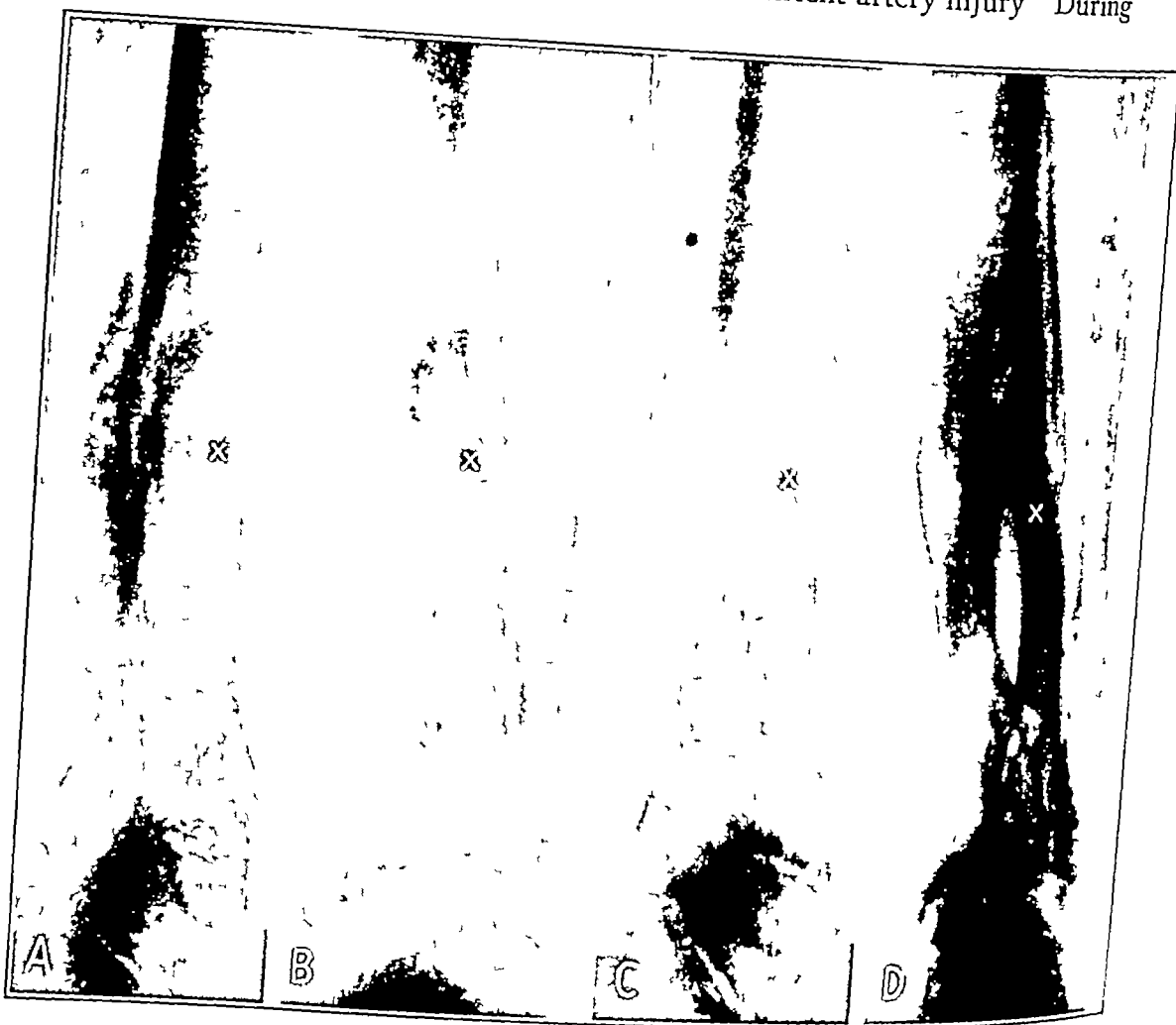


Fig 3 (case 1) — *A* and *B*, condition ten months after injury. The fracture is united, and the dense necrotic fragment (*x*) has been partly replaced by less dense new bone in the lower portion. *C* and *D*, condition two and one-half years after fracture, the necrotic fragment has been replaced by wavy new bone.

operation for nonunion or malposition there is often extensive stripping of periosteum from the ends of the fragment. This appears to make little difference about healing if the operation is otherwise properly performed, and it is difficult to know whether or not the fragment ends have been devitalized. That devitalization may occur is demonstrated by the following case, in which it was found in a bulbous fragment at the fourth operation for nonunion.

CASE 2—A man aged 53 had an ununited fracture of the lower end of the left femur of twenty-eight months' duration. Three attempts had been made by operation to obtain union, without success, the last one four and one-half months previously. There had been primary union of the wound each time. When the fragment ends were bared during a bone grafting operation, the bone of the lower fragment looked pink and viable, but the distal 4.5 cm of the upper fragment, which was enlarged and sclerosed from bony callus, was pale and bloodless. Necrosis was diagnosed, and the end was resected through healthy-appearing bone. On longitudinal section the interior was sclerosed and pale to the same level (fig 4). Microscopic sections revealed necrosis of bone throughout the entire area. There was a good deal of connective tissue invasion, and some dilatation of the cannular systems of the upper necrotic portion was present, but there was little evidence of creeping substitution by new bone. The necrosis had resulted secondarily and had probably followed the stripping of fragment at the last operation, as judged by the small amount of repair in it.

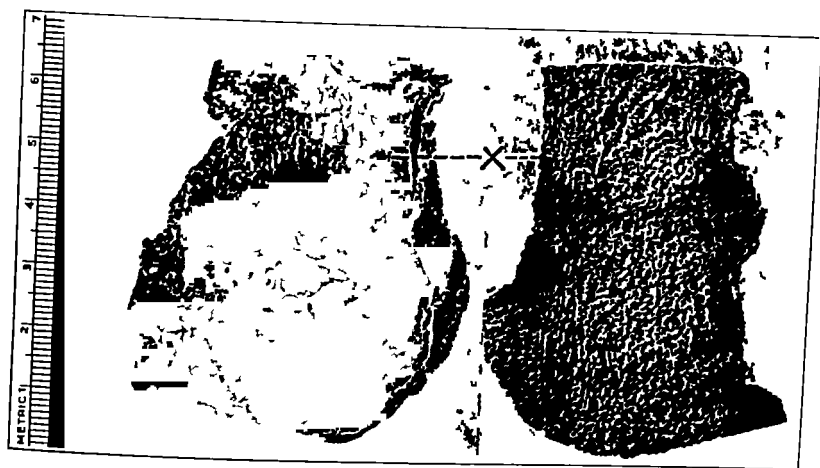


Fig 4 (case 2)—Grayish white aseptic necrotic end (below *x*) of the upper fragment of an ununited fracture, resected at operation

Necrosis of the body of the astragalus following fracture of the neck in 1 case (Dr Dean Lewis) and fracture of the neck with posterior dislocation of the body in another case were previously reported on by me.<sup>9</sup> The diagnosis was based on roentgen evidences of persistence of the original density of the body in the presence of reduced density from atrophy of disuse in the surrounding living bone and of later progressive reduction of density due to creeping substitution. In 1 case there were also irregularity and flattening of the ankle joint surface of the astragalus.

An additional case is reported, in which the head was also necrotic (Dr G T Aitken) and in which pathologic studies were made of the excised astragalus.

CASE 3—A man aged 65 sustained a closed injury to the left ankle in which the neck of the astragalus was fractured and the body posteriorly dislocated (fig 5 *A*). Reduction was accomplished by open operation. There were primary wound healing and prolonged immobilization in a cast, but the ankle remained weak and painful. Roentgenograms taken one year and nineteen days after injury (fig 5, *B* and *C*) revealed the body of the astragalus in the normal position

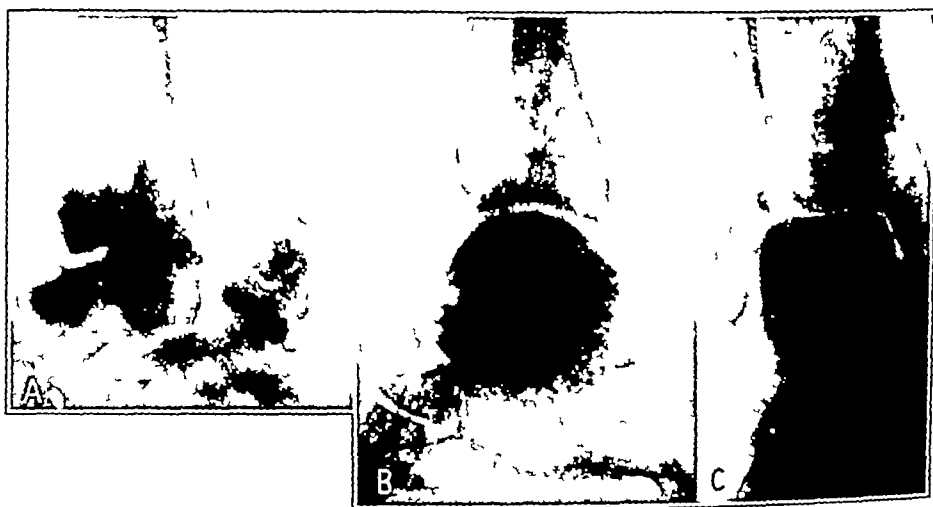


Fig 5 (case 3) —*A*, fresh fracture of the neck of the astragalus with posterior dislocation of the body. Operative reduction followed. *B* and *C*, condition one year and nineteen days later. The fracture is ununited, and the entire astragalus is denser than the surrounding atrophied bones, indicating necrosis.

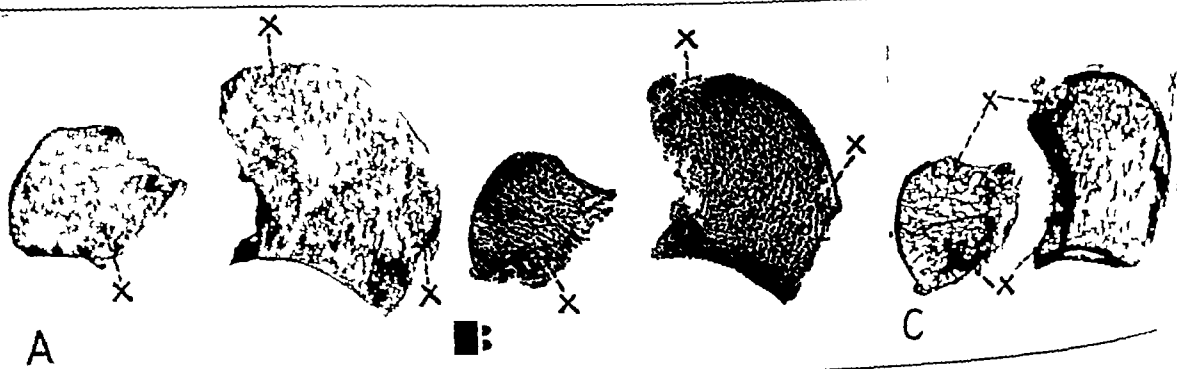


Fig 6 (case 3) —*A*, photograph of cut and fractured surfaces, *B*, roentgenogram of slices, and *C*, microscopic sections of the two dead fragments fifteen months after injury. Fibrous invasion and partial creeping substitution are indicated by *x* in the lower half and upper margin of the head and neck, in the anterior margin along the fracture surface and in the posterior superior part of the body.

but the head laterally displaced and overriding the body, with apparent nonunion. The shadows cast by both the body and most of the head were denser than those of the adjacent bones, which showed evidence of atrophy of disuse. Because of persistent disability, the entire astragalus was excised by Dr G. T. Aitken fifteen months after injury. Examination of the specimen showed that there were



lateral displacement and overriding of the head on the body, with fibrous union of the two. The body had been incompletely fractured during the operative removal.

Figure 6 shows a photograph, a roentgenogram and a stained microscopic section of slices excised sagittally from the two fragments. The lower half of the surface of the body is irregular, owing to a fracture produced during excision. The microscopic section shows the changes best. Both fragments apparently had become necrotic, although it is possible that some of the lower part of the head remained alive. The body fragment still consisted of necrotic bone and marrow except for narrow strips along the posterior superior margin and the whole of the anterior fracture margin, where there had been fibrous invasion and partial creeping substitution by living bone (1). The lower half and the superior margin of the head fragment had also been invaded and partly replaced (1). Figure 7 *A* is a section at the middle of the ankle joint surface of the astragalus showing necrotic bone and marrow and poor staining of the deeper portion of the articular cartilage. The section in figure 7 *B*, from the anterosuperior portion of the body (2), illustrates the process of repair as it crosses the dead bone, the fibrous zone and the zone of creeping substitution.

One reason for the very slight invasion and creeping substitution of the body of the astragalus was the limited number of periosteal surfaces where adhesions could form and give opportunity for blood vessel and osteogenic tissue ingrowth. This could not occur over the extensive cartilage-covered surfaces. In contrast the head, with its greater periosteal surface, was proportionately more invaded and transformed.

The main artery to the astragalus is a branch of the dorsalis pedis artery, which gives branches to the bone along the lateral and inferior junctions of the neck and the body. It is prone to injury in cases of fracture of the neck. If in addition there is complete backward or rotation downward dislocation of the body of the astragalus, the likelihood of aseptic necrosis is greatly increased. This lesion should receive more attention, as it is a cause of nonunion and of poor functional results with fractures of the astragalus.

Fracture of the carpal navicular bone results in severance of the blood supply and necrosis of the proximal fragment in a relatively large percentage of cases. Rarely there is also devitalization of appreciable amounts of the distal fragment. Bony union of the fracture may take place in the presence of aseptic necrosis, but it greatly increases the frequency of nonunion. In the event of bony union, the bone of the dead fragment may be gradually absorbed and replaced by new bone. In some cases central replacement is incomplete, giving the roentgen appearance of cavitation. In other cases the necrotic fragment may

partly collapse. If nonunion results in the presence of necrosis, there are usually much functional disability and atrophy of disuse of the living bone, causing the more dense, nonatrophic necrotic fragment to

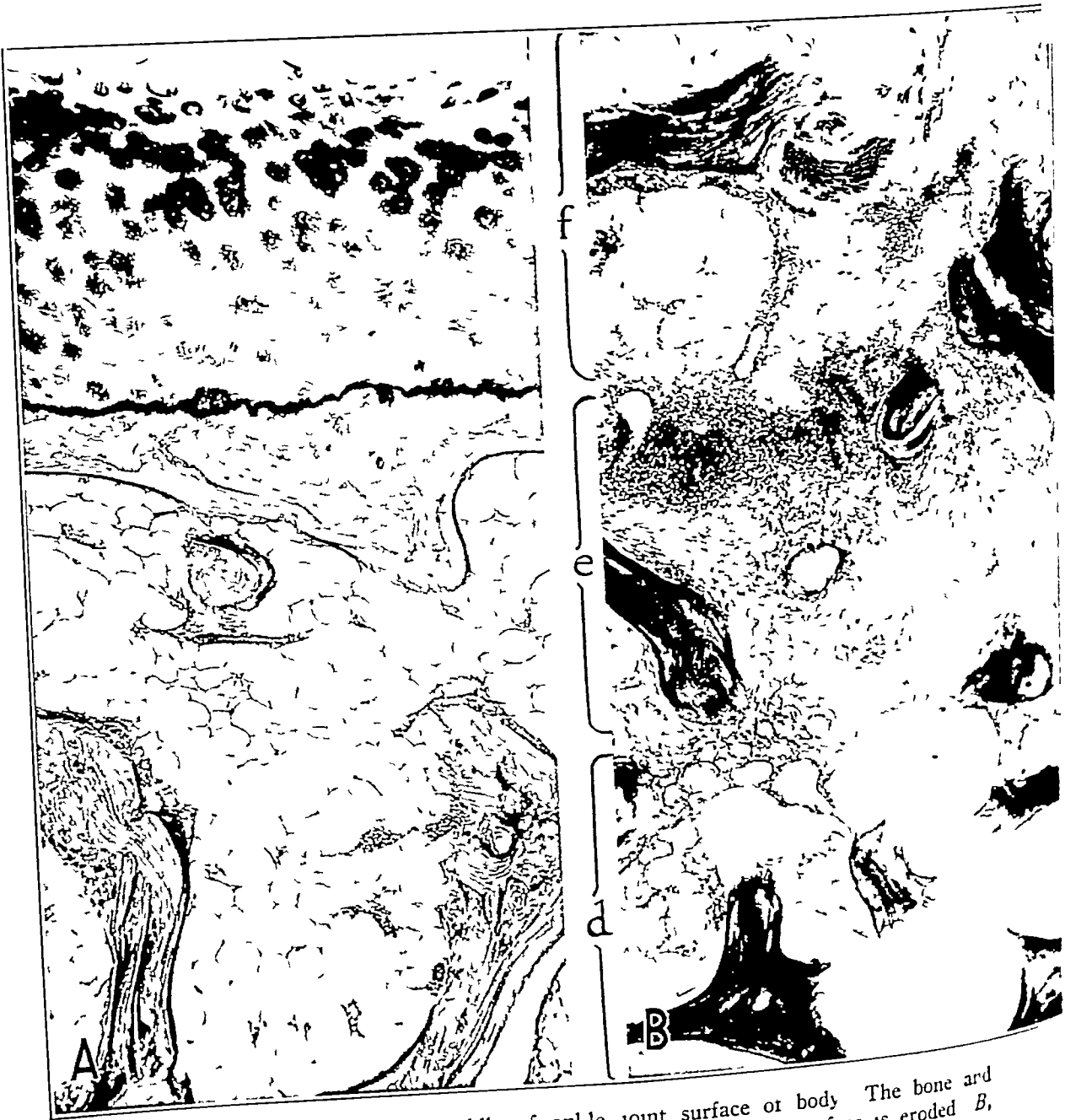


Fig 7 (case 3)—*A*, middle of ankle joint surface or body. The bone and marrow are necrotic. The cartilage stains poorly, and the surface is eroded. *B*, section of the invading zone at  $\tau$  in figure 6, showing (*d*) old dead bone, (*c*) zone of fibrous invasion and (*f*) zone of replacement by new bone and marrow.

stand out in contrast in the roentgenograms. Also, vascular and fibrous invasion and creeping replacement take place at a slow rate, because articular cartilage covers by far the larger part of the surface of the

proximal fragment, which precludes invasion there. These pathologic and roentgen aspects are presented in the following reports:

CASE 4—A man aged 29 sustained a fracture of the right carpal navicular bone, as shown by a roentgenogram taken the same day (fig 8A). The treatment was by immobilization in a cast. In a roentgenogram taken ninety-three days later (fig 8B) there was evidence of nonunion of the fracture and of reduced osseous density from atrophy, except in the proximal fragment (*x*), which retained its original density. The fragment was excised. There was fibrous union of the fracture, and the articular cartilage was grossly little changed except for damage produced in removal.

In a microscopic section (fig 9A) the bone and marrow were seen to be necrotic and free from invasion except at one edge (*r*), where there were a small



Fig 8 (case 4) —A, recent fracture of navicular bone. B, condition ninety-three days after injury. There was nonunion of the fracture, the necrotic proximal fragment (*x*) possesses greater density than the surrounding living bones, which show atrophy from disuse.

amount of fibrous ingrowth and partial replacement of dead bone by new bone (fig 9B). Cartilage staining was somewhat reduced.

If the necrotic fragment is not removed it may undergo slow creeping substitution, or the interior may be absorbed but not replaced by bone, giving a honeycombed appearance in the roentgenograms. Adhesions, partial necrosis of cartilage, irregularity of articular surface and chronic arthritis are frequent late results, as is shown by the reports of Speed and others.<sup>13</sup>

13 Speed, K. Fractures of the Carpus. *J Bone & Joint Surg* 17:965, 1935.  
A Text-Book of Fractures and Dislocations, ed 3 Philadelphia: Lea & Febiger, 1935.

Intra-articular fracture of a normal bone with complete separation of a fragment consisting of bone and articular cartilage is most frequently seen in cases of fracture of the head of the radius and of the lower articular surface of the humerus, but it may occur in other regions, such as the head of the femur, where a chip is detached. If the detached fragment is entirely displaced from its bed, it rarely remains a free body but becomes attached to the lining of the joint. In this useless position it



Fig 9 (case 4) —Excised necrotic fragment of navicular bone *A*, microscopic section, cartilage staining is slightly diminished. The bone and marrow are necrotic except at  $\times$ , where beginning invasion and replacement may be noted. *B*, high power photomicrograph taken at  $\times$ , showing connective tissue and blood vessel invasion and beginning replacement by new bone and marrow.

has no supporting function to perform, consequently, although it becomes revascularized and gradually replaced, the replacing tissue contains much less bone than when the fragment becomes united in a useful position. Eventually it may be largely absorbed. At the articular end of the humerus the capitellum, in some cases with a portion of the trochlea is detached, rotated and displaced anteriorly and upward, where it becomes attached and imperfectly replaced by new bone, as in the following case.

CASE 5—A man had been injured six months previously. Roentgenograms (fig 10) revealed the anteriorly displaced and rotated condyles with both their cortical and their cancellous bone casting shadows greatly reduced in density. At operation the cartilaginous surface of the fragment was loosely adherent to the

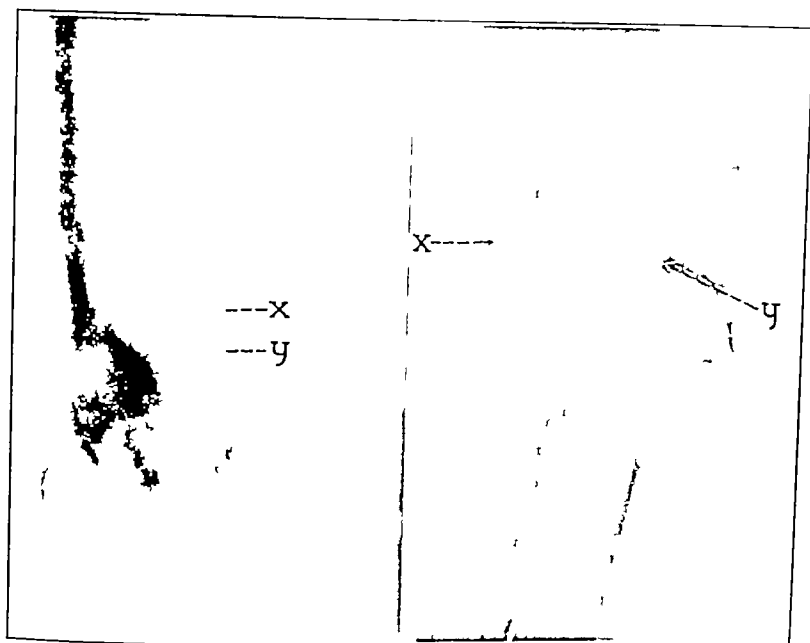


Fig 10 (case 5)—Six month old intra-articular fracture of the capitellum and part of the trochlea of the humerus with forward and upward displacement and bony attachment within joint. Note (x) the capitellum and (y) the trochlea

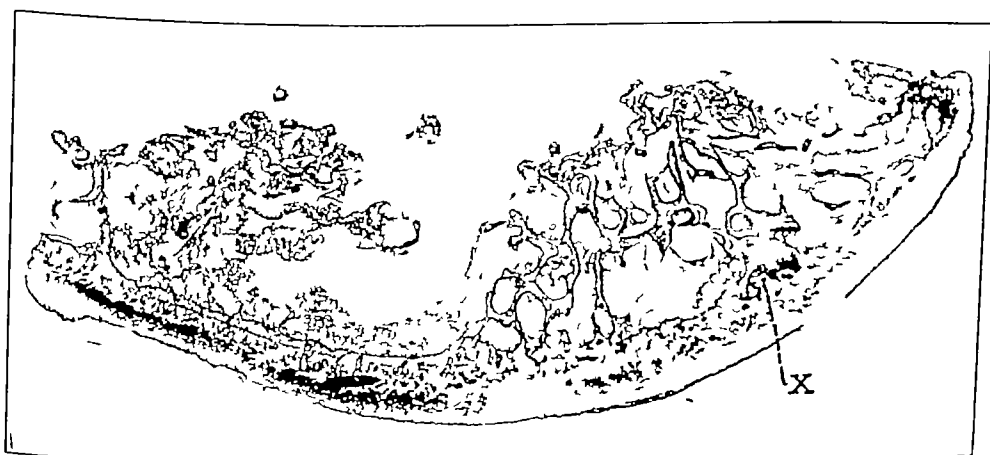


Fig 11 (case 5)—Section of excised capitellum. The heavily trabeculated portion is old dead bone; the rest is delicate new replacement bone and marrow. The cartilage is intact, but staining is impaired in parts.

synovial lining, and its base was united by bone to the underlying cortex. It was excised and found to consist grossly of cartilage that was little changed and of bone that was extremely porous and filled mainly with fatty marrow. A microscopic section (fig 11) showed only a small amount of the old heavy trabeculated bone left, which was necrotic and had fibrous invasion of its marrow spaces



Fig 12 (case 5) —Higher magnification at  $\tau$  of figure 11, showing the zone of creeping replacement of dead bone ( $c$ ) by new bone ( $d$ ). Most of the cartilage cells stain.

It extended to the cartilage only at  $\tau$ , and creeping substitution was in progress along its periphery. The rest of the cortex and trabeculated bone had been replaced by extremely delicate new bone. The marrow was composed of fat, a loose connective tissue framework and scattered hemopoietic cells. Figure 12 shows the region ( $\tau$ ), with dead bone, and fibrous marrow being replaced by

new bone The cartilage here and elsewhere, with regenerated blood vessels along its underlying surface, showed normal staining of the majority of nuclei Had this fragment not been excised there would no doubt have been later absorption of cartilage and further removal of bone

A similar fracture was seen in which only slight anterior rotation displacement resulted There was bony union ten months later, with the condyles functioning and casting shadows of normal density In the presence of activity they had apparently been replaced by a normal amount of bone

Interruption of the blood supply with subsequent necrosis of the head of the femur produced by fractures of the intracapsular portion of the neck has already been so fully reported on<sup>14</sup> that it will not be reviewed in detail It constitutes by far the most important lesion produced by interruption of the circulation in bone, because of its great frequency and because of its adverse effects, which are still all too little realized by the members of the medical profession The blood supply of the head of the femur is derived from arteries which reach it principally by way of the capsule of the neck, especially posteriorly and by way of the round ligament There appears to be a good deal of variation in the blood supply coming from each set of vessels and also in the extent of collateral circulation between the two The indications are that in adults end arteries are more common in the head of the femur than in any other part of the skeleton, and necrosis from causes other than trauma is often located here

In case of death of the head from injury to the vessels, the fracture may either unite or remain ununited Union of the fracture is much more apt to occur if it is impacted or if there are accurate reduction and operative fixation It occurs by formation of a fibrous callus in the cancellous spaces of the distal end of the neck, which grows across the fracture line and into the cancellous spaces of the proximal fragment No periosteal or peripheral callus forms, and the fibrous callus is transformed directly into bone without the appearance of cartilage in the process, as was recently pointed out by Felsenreich<sup>15</sup> Vascularized connective tissue then begins to invade the head and to break down and replace the dead marrow The invasion may take place from the callus which bridges the fracture line, from portions of capsule which may remain ununited and from the round ligament Metaplasia of the invading

14 (a) Santos, J V Changes in the Head of the Femur After Complete Intracapsular Fracture of the Neck Their Bearing on Non Union and Treatment, *Arch Surg* 21 470 (Sept.) 1930 (b) Phemister D B Fractures of Neck of Femur, Dislocations of Hip and Obscure Vascular Disturbances Producing Aseptic Necrosis of Head of Femur *Surg, Gynec & Obst.* 59 415 1934 The Pathology of Ununited Fractures of the Neck of the Femur with Special Reference to the Head of Bone & Joint Surg 21 681 1939

15 Felsenreich Histologische Untersuchungen an operierten Schenkelhalsbrüchen, *Arch f klin Chir* 192 490, 1938

connective tissue or fibrous callus into new bone and bone marrow is soon established and progresses into the head simultaneously with and a short distance back of the fibrous invasion. This creeping replacement occurs gradually, and the neck is transformed soon after the healing of the fracture. But the head is usually still mainly untransformed at the completion of bony union of the fracture, and the process may continue for months or years before it is either completed or comes to a standstill. The new bone which replaces the dead bone after union is complete and some function has returned to the limb is soon about as dense as the old bone, for which reason it is difficult to recognize creeping substitution following fracture with bony union in roentgenograms. In how many cases the condition may go on to unrecognized complete reorganization is not known.

When the condition is recognized it is usually because of collapse of the superior untransformed portion of the head from premature weight bearing or because of late chronic arthritis. Collapse of the head may begin at any time from a few months to two or three years after healing of the fracture. The broken-down portion may be invaded and replaced by new bone in the course of time. But if an ununited fracture line is established between the broken-down and the transformed portions, the replacement may be greatly retarded, as in the following case, in which the rare opportunity was presented of confirming the roentgen diagnosis by pathologic examination.

CASE 6 (Dr. Carl Badgley).—A woman had an impacted fracture of the neck of the femur (fig. 13 *A*), which was treated by rest. Bony union resulted. After walking was resumed, pain, stiffness and weakness set in and gradually progressed until, four years and two months later, she was badly crippled. A roentgenogram taken then (fig. 13 *B*) showed a dense, wedge-shaped area (*v*) extensively separated from the surrounding bone. The rest of the head cast mottled shadows and had a hazy articular cortex as compared with the early picture (*A*), which indicated transformation. The upper portion of the head was excised.

A microscopic section through most of the excised portion (fig. 14) included the broken-off wedge, which was separated from the surrounding bone by an irregular band of fibrous tissue at the left and at the base and a pseudoarthrotic line at the right. Its left edge was separated from the rest by a pseudoarthrotic cleft and consisted of substituted new bone covered by a thin layer of fibrocartilage. The main part of the wedge was capped by old articular cartilage of normal thickness, with the cells staining poorly and the matrix partly calcified. Underlying it, from (*d* to *e*), were old dead bone and dead marrow, with a small amount of bone dust which had been ground into its cancellous spaces. To the left of *e* was old dead bone which had been invaded by fibrous marrow, and at the deepest portion there had been some replacement by new bone. Figure 15 is a high power photomicrograph taken at *d*, showing the dead bone and marrow in the portion (*a*) and fibrous marrow throughout the dead bone (*b*) which was spreading into and replacing the dead marrow at *a*. Replacement of the dead bone by new bone had not yet started at *b* but was present farther to the left. Figure 16 *c*



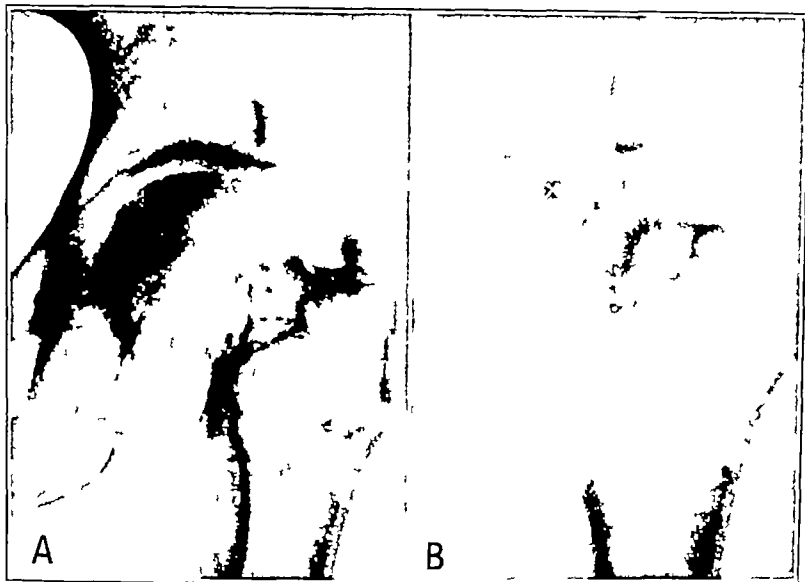


Fig 13 (case 6) —*A*, recent impacted fracture of the neck of the femur *B*, condition four years and two months later. The neck fracture is united. The head, which became necrotic, is flattened. The wedge-shaped remaining dead portion (*x*), with the original density and articular cortex preserved, is separated from the substituted portion, which is mottled and has a hazy shadow of new articular cortex.



Fig 14 (case 6) —Microscopic section of necrotic wedge (base *a-b* and apex *c*) extensively separated from the transformed portion by fibrous tissue like that of an ununited fracture line.



Fig 15 (case 6) —High power photomicrograph of the necrotic wedge at *d* of figure 14, showing (a) dead bone and dead marrow uninvaded and (b) dead bone in which fibrous tissue has invaded and replaced the dead marrow



Fig 16 (case 6) —Pseudarthrotic fracture line at *e* in figure 14, separating (a) from (b). The fracture line contains some bone dust in the marrow spaces (a) from the

(through the pseudoarthrotic junction) shows necrotic bone and marrow infiltrated with some bone dust (*a*) and living bone (*b*) outside the necrotic area. The articular cartilage beyond the limits of the wedge consisted of a narrowed layer of fibrocartilage, and its underlying cortex was thin and uneven, showing that both had been transformed.

The following case is remarkable in its bearing on several aspects of devitalization of the head in fractures of the neck of the femur.

CASE 7—A 96 year old woman sustained an impacted intracapsular fracture of the left hip (fig 17 *A*). Treatment was by rest in bed, and the fracture united. She remained in bed for more than a year but after one and one-half years began to walk. Function gradually returned to normal, and she continued to be active until four years after the injury, when she again fell, fracturing the base of the neck of the right femur. Figure 17 *B* shows the roentgen appearance of

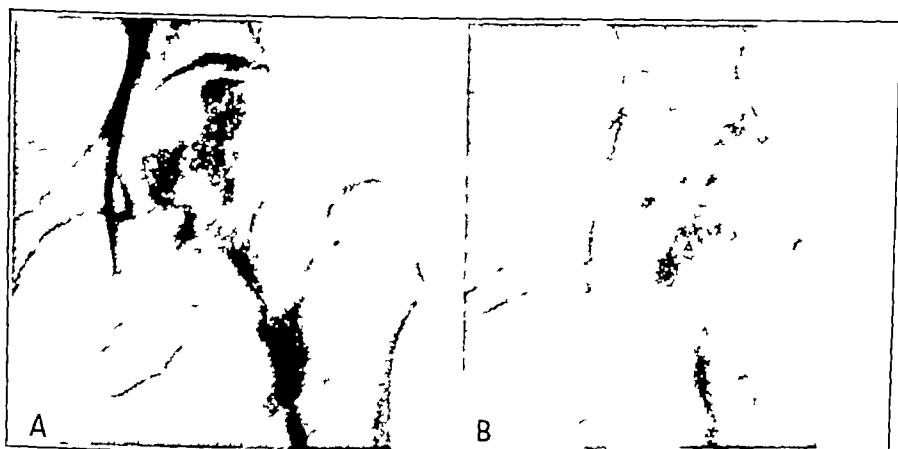


Fig 17 (case 7)—*A*, fresh impacted fracture of the neck of the femur in a 96 year old woman. *B*, condition three and three-fourths years later. The fracture is united. The mottled trabeculae in the head suggest transformation.

the left hip three and three-fourths years after the fracture. The patient was bed-ridden after the fracture of the right hip until she died, four years later, at the age of 104 years, of carcinoma of the left breast.

At necropsy both hips were obtained. The right hip presented a normal picture aside from moderate coxa vara due to the healed fracture at the base of the neck (fig 19 *A*). Microscopically the head was alive but atrophic, and the cartilage and synovia were intact except for senile changes. The left hip (fig 18) showed bony union of the fracture. There was hiping at the margins of the articular cartilage of the head, most marked posteriorly (*A*). The cartilage was thinned and roughened in its weight-bearing portion but fairly well preserved mesially below the fovea and laterally beyond the line of contact with the acetabulum. The cartilage of the acetabulum was also somewhat roughened, thinned at its superolateral margin and fibrous in parts of its lower extent. There were one osteo cartilaginous body free in the joint and two attached to the round ligament by narrow pedicles. There were two islands of ossification in the interior portion of

the capsule and one in the round ligament. There were a few villous tags of the synovial lining. A slice 0.66 cm thick was cut through the center of the femur and acetabulum. The cut surface of the head revealed in its inferomesial portion

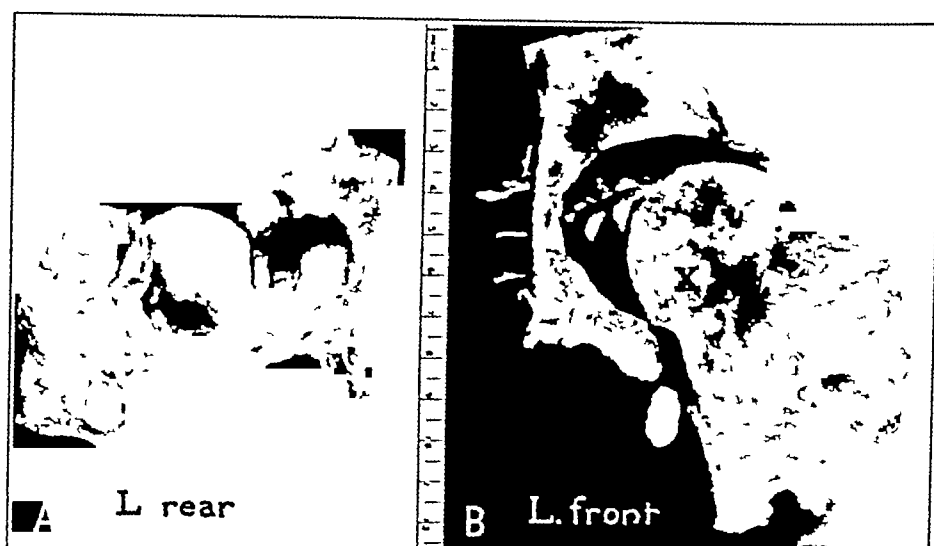


Fig 18 (case 7) —Necropsy specimens of the left hip eight years after fracture of the neck followed by bony union. *A*, posterior view, *B*, coronal section. Marginal chipping, osteocartilaginous loose bodies and cartilage erosion may be noted. The necrotic area is shown at *x*.

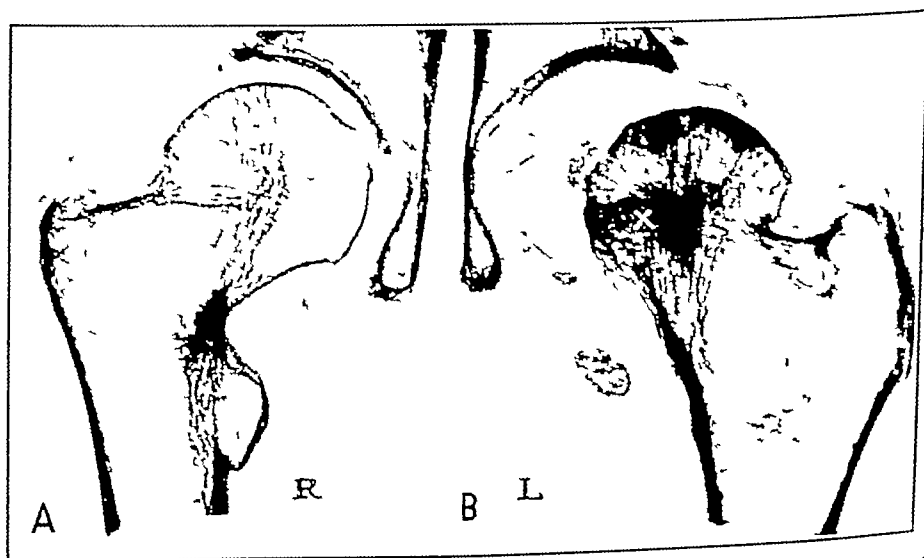


Fig 19 (case 7) —Roentgenogram of slices of the hips. *A*, healed fracture of the right hip at the base of the neck, the head survived. *B*, healed intracapsular fracture of the neck (left hip). The head became necrotic and transformed except at *x*. Note the shadows of osteocartilaginous loose bodies.

a whitish, circumscribed, necrotic-appearing area (fig 18, *x*). A roentgenogram of the slice (fig 19, *L*) shows the head in a slight valgus position as a result of the old lateral impaction. The light area (*r*) shows a narrow irregular ring

of increased density about it. The head cast dense shadows in the direction of the lines of stress and in the cortical and subcortical regions. There was increased density in the cortical and subcortical regions of the weight-bearing portion of the acetabulum. These changes were in marked contrast with those in the right hip (*R*). A microscopic section of the hip (fig 20) revealed living bone throughout the head except at *x* and beneath the thick cartilage at the top of the head. In the latter region a small stretch of old cortex and of underlying heavy trabeculae were necrotic, and their cancellous spaces were filled with fibrous marrow. The lesion (*x*), which is seen magnified in figure 22 *A*, consisted of a central mass of necrotic bone and bone marrow which was immediately surrounded by a narrow calcified zone outside which was a thicker fibrous zone containing necrotic bony trabeculae. External to the fibrous zone were living bone and marrow, and along the surface were very slight indications of creeping substitution. This encapsulat-



Fig 20 (case 7)—Microscopic section of the left hip, showing mottled trabeculae and walled-off necrotic area (*x*) in the head and chronic arthritis and a loose body in the joint.

ing zone is shown in high power in figure 21 *A*. The necrotic area resembled the one (fig 22 *B*) from a case of ununited fracture of the neck with death of the head of four and one-half years' standing. Here the zone of transformation was not calcified, but creeping substitution had almost come to a standstill in it. The articular cartilage of the head in the weight-bearing region was markedly thinned and frayed (fig 21 *B*). Over the lateral portion of the head and beneath the fovea it was of normal thickness but stained poorly. Beneath the fovea the bone had penetrated into the cartilage from within and partly replaced it. The loose bodies attached to the ligamentum teres consisted of a mixture of hyaline and calcified cartilage and of cancellous bone. The free body contained only hyaline

and calcified cartilage. A microscopic section of the synovial lining showed slight villous formation and fibrous thickening.

In summary, an impacted fracture of the neck of the left femur in a 96 year old woman appears to have cut off the blood supply and resulted in necrosis of the head. Bony union followed, and in the

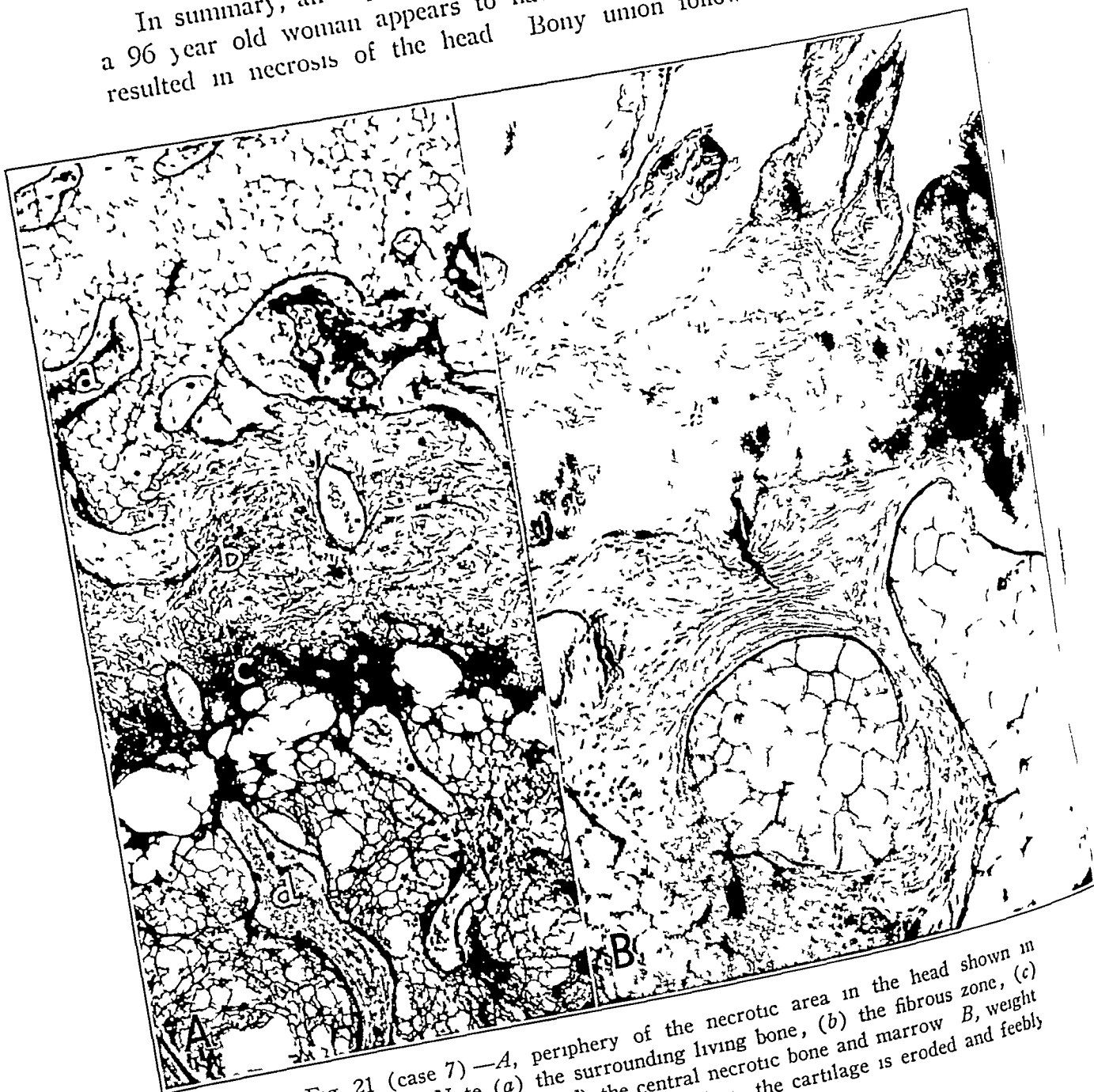


Fig 21 (case 7) —A, periphery of the necrotic area in the head shown in figure 21 (x). Note (a) the surrounding living bone, (b) the fibrous zone, (c) the inner calcified zone, and (d) the central necrotic bone and marrow. B, weight bearing surface of the head. The bone is alive, the cartilage is eroded and feebly staining.

absence of weight bearing for one and one-half years most of the head underwent replacement by living bone. Subsequent weight bearing did not cause collapse of the head. In the inferior and mesial portion replace-

ment came practically to a standstill, leaving, eight years after fracture, a necrotic island the fibrous capsule of which had calcified in its inner portion. There were necrosis and erosion of some of the articular cartilage and secondary formation of arthritis deformans and of osteo-cartilaginous loose bodies. The case offers proof of the fact that if weight bearing is avoided for many months after fracture there may be sufficient creeping replacement by new bone to prevent subsequent collapse of the

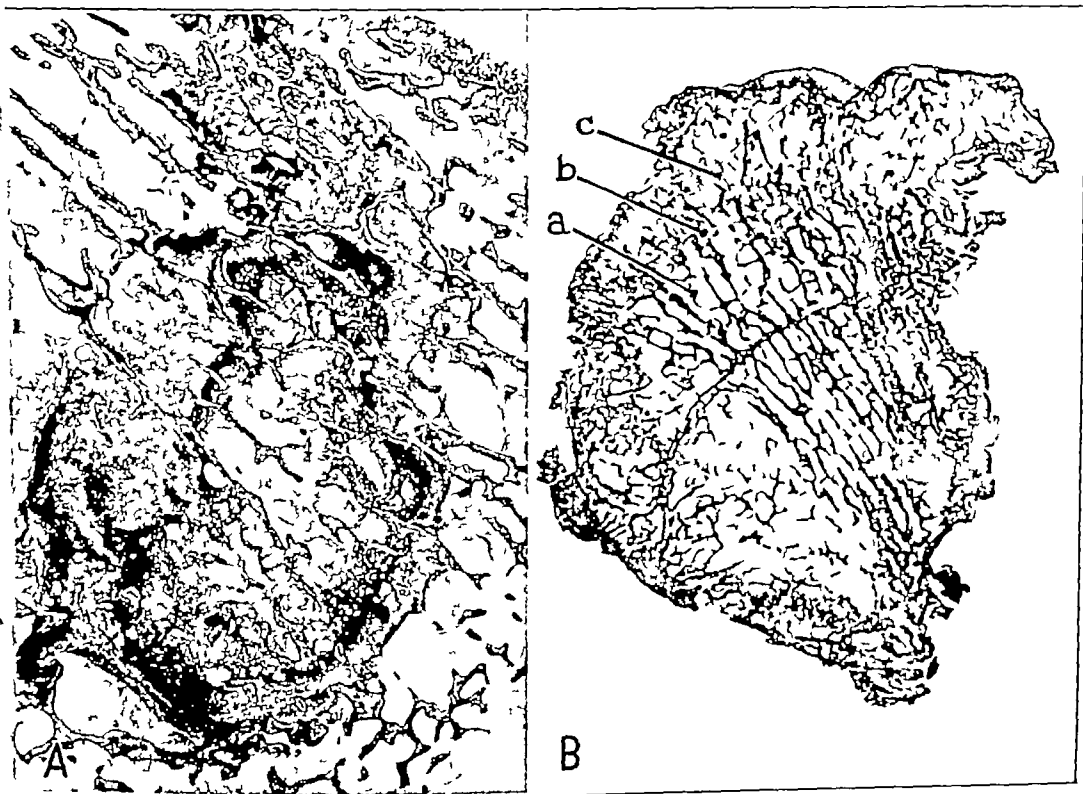


Fig 22 (case 7) —A another section of the walled-off necrotic area shown in figure 20 B, section of the head in the case of a four and one-half year old ununited fracture of the neck. There is a similar central necrotic area (a) surrounded by a fibrous zone of transformation (b) and then by substituted new bone (c)  $\times 3$

head, it also shows that arthritis deformans may be a sequel of necrosis of the head without collapse of the weight-bearing portion.

Necrosis of the head associated with nonunion of the fracture of the neck has been studied at all stages, from a few days to many years after the injury. The changes may be summarized as follows. The entire bony head becomes necrotic in the great majority of cases, including the bone

and the bone marrow. Atrophy from disuse develops in the adjacent living bone, and in six to eight weeks the dead head is so much denser than the living bone that it casts a heavier shadow in roentgenograms. Revascularization and fibrous tissue infiltration of the marrow spaces begin within a few days to weeks by way of the round ligament, adhesions or any remaining untorn portion of the capsule. This usually



Fig 23 (case 8) —SIX month old ununited intracapsular fracture of the neck. The density of the head is normal in its upper portion and irregularly reduced mesially and inferiorly (r). This indicates a necrotic head with partial substitution by new bone.

progresses slowly and is followed by a zone of metaplasia in which there is absorption of the old dead bone and creeping replacement by a less dense new bone than is laid down when the fracture unites. A head in the process of replacement was studied in the following case.

CASE 8—A 52 year old man fractured the left hip six months before admission. A roentgenogram (fig 23) revealed nonunion with rotation of the head and



irregular reduction in density in its inferior and mesial portions as compared with the more uniform superior portion "Disuse atrophy" of the lower fragment was seen The head was excised, and a Whitman reconstruction operation was performed There were whitish calcium deposits in large synovial villi, in the untorn portions of the capsule and in the round ligament A roentgenogram and a microscopic section were made of a slice cut coronally from the head (fig 24) The roentgenogram shows marked reduction in density lateral to the fovea, with extensions upward, laterally and irregularly downward In the superior and inferolateral regions the shadows of trabeculae were of even density and appeared to be unchanged

On comparison of the roentgenograms with the microscopic section (*b*) it is seen that there were a large area at the top and a small area at the bottom of old dead bone and marrow (*c*) bordered by a zone of fibrous invasion and creep-

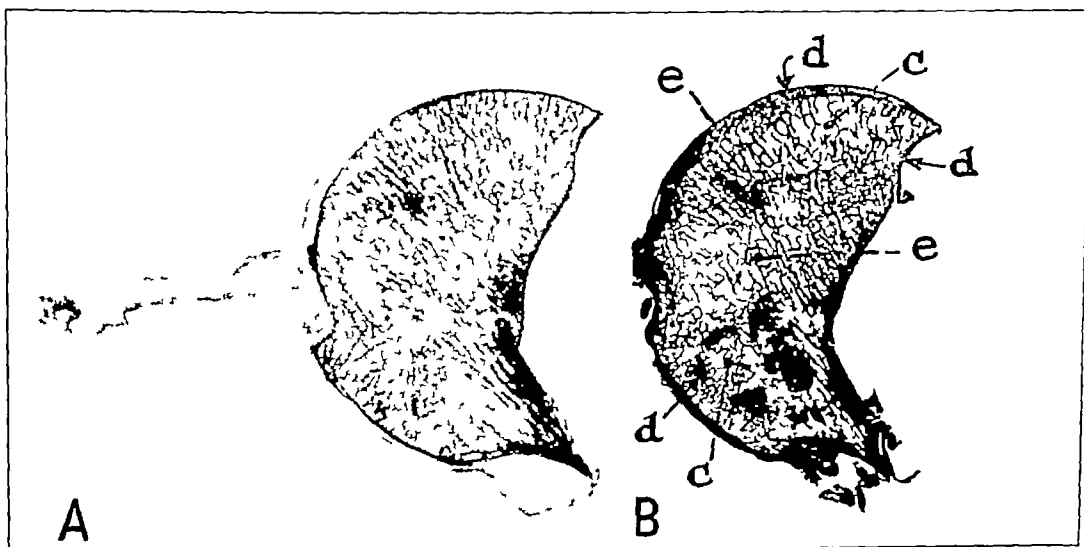


Fig 24 (case 8) —*A*, roentgenogram of a slice of the excised head The round ligament is partly calcified There is mottled reduction in density in regions where dead bone is replaced by new bone, especially about the fovea *B*, microscopic section of the head Note (*c*) the uninvaded dead regions, (*d*) the zones of invasion and replacement and (*e*) the substituted living region

ing substitution (*d*) The rest of the section (*c*) had undergone invasion and extensive creeping replacement by a more spongy living bone and living marrow, although along the middle and inferior portions of the eroded fracture surface there were old dead trabeculae, which accounted for the greater density The cartilage was grossly intact, but microscopically its staining properties were reduced, however, the cartilage cells stained much better in the regions where the underlying bone had been revascularized and substituted than over the dead area at the superior portion Figure 25 shows regions *c*, *d* and *e* in greater magnification

Transformation was taking place rather rapidly in this head and in the plane of the microscopic section only about one third of the old dead

bone and marrow remained uninvaded. Microscopic sections of the round ligament revealed several hair-sized blood vessels which probably had hypertrophied and were supplying blood to the head. A unique observation was the calcium deposits in the round ligament and in synovial villi in richly cellular areas of connective tissue.

That operation in a case of ununited tracture with necrosis of the head may result in a successful outcome with rapid replacement of the remaining dead bone is illustrated by the following case

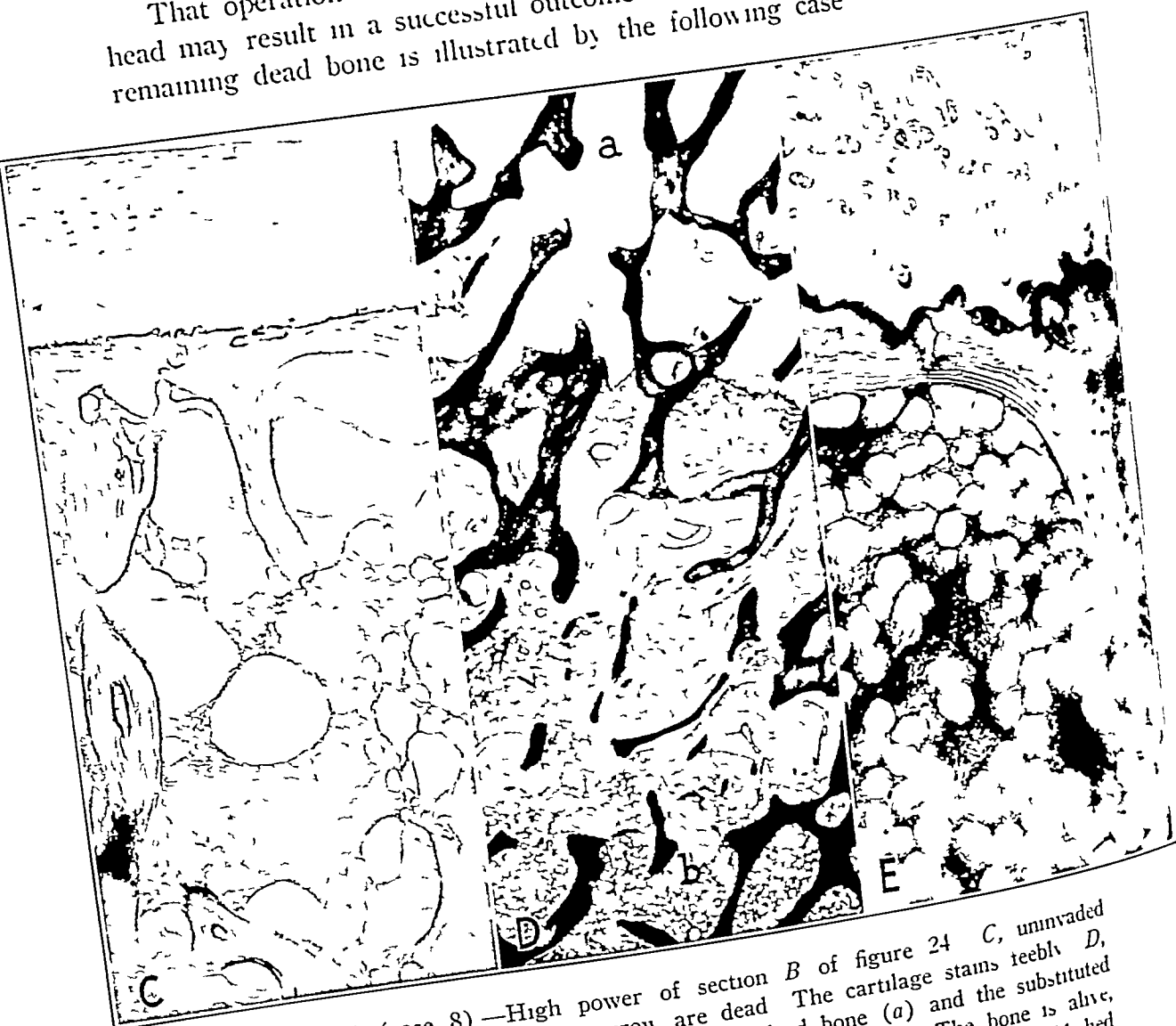


Fig 25 (case 8)—High power of section B of figure 24. C, uninvaded upper portion, the bone and marrow are dead. The cartilage stains feebly. D, zone of invasion and replacement. Note the dead bone (a) and the substituted new bone (b). E, a cortical field of the replaced region. The bone is alive, and the cartilage stains fairly well, with its nutrition improved by the reestablished underlying circulation.

CASE 9—A woman aged 52 had an ununited fracture of ten months' duration. A roentgenogram (fig 26 A) showed areas of markedly reduced density in the lower portion of the head and an even shadow or about the normal density in

the upper portion of the head. Between the two and bordering on the eroded surface was an irregular zone of increased density. The findings indicated that there was death without invasion and replacement of the upper part of the head, creeping substitution of the lower part and possibly eroded bone meal infiltration of the marrow spaces between, accounting for the increased density. The fracture was operated on by insertion of two bone grafts and three threaded wires for fixation, after the method of Compere<sup>16</sup>. Figure 26 *B* shows the appearance after two months and figure 26 *C* the appearance after thirteen and one-half months, the wires having been removed five months previously. The fracture had united, and the upper necrotic portion of the head, which had been extensively bored and replaced by the transplants, appeared to have been replaced by living bone with preservation of the normal contour. The patient used crutches for ten months, after which there was weight bearing, with excellent results.

Long-standing ununited fracture of the neck of the femur with necrosis of the head is also not infrequently complicated by cartilage

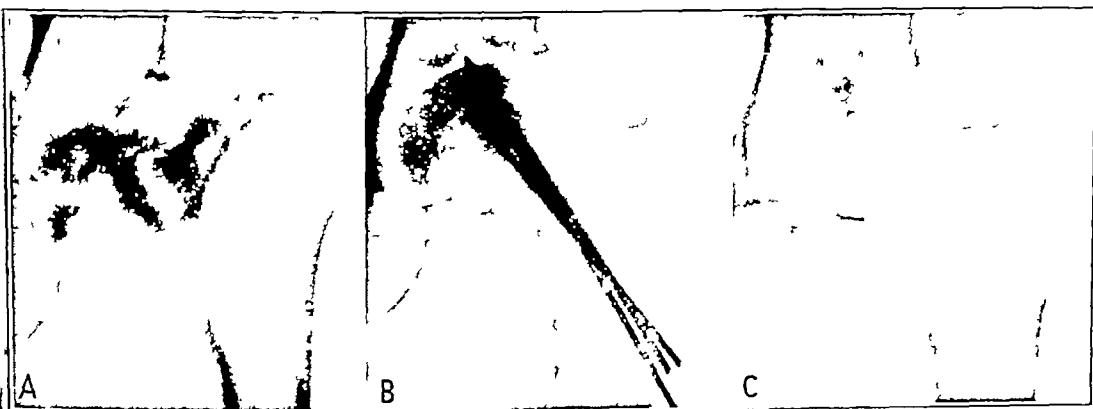


Fig. 26 (case 9)—*A*, ununited fracture ten months old, with death of the head and about one half of it substituted for by less dense new bone. The upper portion is dense old dead bone. The lower portion is spongy new bone. *B*, condition thirty days after fixation by three threaded wires and two bone grafts. *C*, condition thirteen and one-half months after operation and five months after removal of the wires. The fracture is united and the head largely transformed.

adhesions, osteocartilaginous loose bodies and mild synovial changes of arthritis deformans. If there is complete absorption of the necrotic area the interior of the head may contain few trabeculae and give the roentgen appearance of a cavity. If the replacement comes to a standstill, the necrotic area located centrally or in the superior portion may continue to cast a dense shadow for years, as in the case illustrated by figure 22 *B*.

16 Compere, E. L. The Restoration of Physiological and Anatomical Function in Old Ununited Intracapsular Fractures of the Neck of the Femur. *J. Bone & Joint Surg.* 22: 261, 1940.

## DISLOCATIONS

Poor functional results following traumatic dislocations of the hip were reported by the older surgeons and attributed to chronic arthritis. It was not until after Axhausen described fracture of the neck of the femur followed by necrosis of the head, bony union and subsequent collapse of the head that the bad results following dislocation of the hip were recognized as due to necrosis of the head. Mueller reported the first case in 1924,<sup>1</sup> and since then the condition has been recognized with increasing frequency. In the cases in which diagnosis has been made the changes have been similar to those associated with fracture of the neck with necrosis of the head, bony union and subsequent breaking down of the head. After reduction of the dislocation there is sometimes a period of several months to a year of relative freedom from symptoms and a normal roentgen picture. Then weakness, stiffness and pain set in and gradually progress, and roentgenograms reveal the changes. Banks<sup>17</sup> has recently reviewed 11 cases studied in this department or in consultation and has collected 39 cases reported in the literature. Among the patients were 8 children, in all of whom there was transformation of the head, with good results. In practically all of the 42 cases of fracture in adults the joint remained markedly deformed, and the functional results were poor. The cause of the necrosis has not been definitely determined. The round ligament was torn in all cases, whether or not there was an associated fracture of the acetabulum. When it constitutes an important source of blood supply to the head, the necrosis may result from its tear. It is possible, however, that the anterior or posterior circumflex arteries to the neck are also injured in the dislocation. The following case illustrates the changes.

CASE 12—A man aged 61, seen in consultation with Dr W B Carroll, had dislocated the right hip twenty-six years previously. The dislocation had been reduced, and there had been complete restoration of function, which had persisted. Recent roentgenograms had shown a normal appearance of the right hip. Eighteen months previously the patient had suffered a dislocation of the left hip with fracture of the posterior acetabular margin (fig 27A). Eighty-one days after reduction the head of the femur appeared normal in roentgenograms. Weight bearing was then resumed, but the hip gradually became more painful and restricted in motion. A roentgenogram taken nine months after the injury revealed beginning deformity of the head. Despite the use of a walking caliper

<sup>17</sup> Banks, S. Aseptic Necrosis of Femoral Head Following Traumatic Dislocation of the Hip, *J Bone & Joint Surg*, to be published.

splint, this increased and figure 27 *C* shows the result eighteen months after injury. Necrosis of the head is doubtless the usual explanation of "chronic arthritis" following dislocation of the hip.

About the only other dislocation to result in interruption of the blood supply of the bone without associated fracture is that of the carpal lunatum. When this bone is completely dislocated anteriorly all of its dorsal attachments are torn, and, since the blood supply comes mainly through them, its circulation is usually interrupted, and the bone becomes necrotic. The displaced bone is in a more or less useless position, and if it remains there for a long time it eventually undergoes creeping substitution by bone of greatly reduced density similar to that of the



Fig 27 (case 10) —*A*, recent dislocation of the hip, with a chip off the posterior acetabular margin. *B*, condition eighty-one days after reduction. *C*, condition eighteen months later.

broken-off and displaced condyles of the lower end of the humerus in case 5 (fig 11).

A not uncommon injury is that of fracture of the navicular bone, with perilunar carpal luxation in which the lunatum and the proximal fragment of the navicular bone are subluxated anteriorly, while the remaining bones of the carpus are subluxated posteriorly. The blood supply of both the proximal navicular fragment and the lunatum may be interrupted, with resultant necrosis. This is illustrated in the following case.

CASE 11—A man 29 years old injured his wrist thirty-eight days before examination. Figure 28 *A* reveals the roentgen appearance at that time. The hand had been in a splint, and the bones surrounding the anteriorly subluxated

lunatum and the proximal fragment of the navicular bone were atrophic and cast slightly fainter shadows than the latter. The dislocation was then reduced by open operation, and the wrist was immobilized for eight weeks. A roentgenogram taken ninety-six days after injury (fig 28 *B*) showed that the lunatum and the adjacent navicular fragment had retained their original density, while the surrounding bones were still more markedly atrophic and reduced in density and the fracture was ununited. Excision of the necrotic bones was advised, but the patient refused operation.

Late changes similar to those associated with Kienbock's disease should be anticipated in cases of reduced dislocation of the lunatum.

Arthroplasty of the hip joint has not infrequently resulted in good restoration of free motion, but after weight bearing is resumed the joint slowly breaks down, with erosion of much of the remaining portion of the head and sometimes of part of the neck of the femur. The end result is a poorly functioning and frequently painful hip with varying degrees



Fig 28 (case 11) —Necrosis of the dislocated lunatum and proximal fragment of the navicular bone. *A*, thirty-eight days after injury. Note the slightly reduced density of the other bones from atrophy. *B*, ninety-six days after injury. Note the markedly reduced density of the other bones from atrophy, causing the unatrophied lunatum and navicular fragment to stand out.

of restriction of motion. In some cases, as that reported by me,<sup>14b</sup> the roentgen evidences of necrosis of the remaining portion of the head are very striking, and the subsequent reduction in size and invasion and replacement of the dense necrotic bone by new bone can be followed in roentgenograms. The reason for necrosis is that conditions similar to that of dislocation of the hip are created by the operation. In fact, the likelihood that capital necrosis will follow arthroplasty should be greater than the likelihood that it will follow dislocation, since the practice advocated by Murphy of excising the capsule of the neck which contains blood vessels going to the head, has been extensively followed. Instead of excising the capsule of the neck, every effort should be made not to

disturb it and to preserve the blood supply of the detached and refashioned head. In the following case of arthroplasty the indications are that the head disappeared rapidly as a result of erosion following aseptic necrosis.

CASE 12—A woman aged 34 had bony ankylosis of the right hip following infectious arthritis two years previously, which had healed without drainage. During arthroplasty the capsule of the neck was excised, and the head was capped by free fascia lata. The wound healed by primary union and figure 29 shows the roentgen appearances twenty-two days, nine and one-half months and two and one-third years respectively after operation. As the head was eroded, the weakness and disability in the joint increased, and, although motion was free, the patient resorted to the use of a crutch two years after operation. Too little attention has been paid to aseptic necrosis as a cause of bad results following arthroplasty.

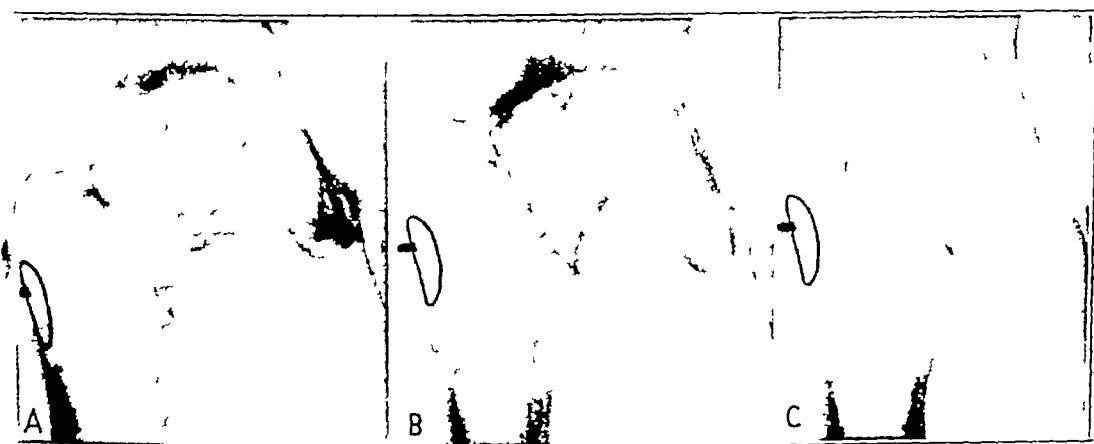


Fig 29 (case 12) —Necrosis and erosion of the head of the femur following arthroplasty. *A*, twenty-two days after operation, *B*, nine and one-half months after operation, the uneroded portion of the head is slightly denser than the atrophied trochanter and neck, *C*, two and one-third years after operation.

#### SUMMARY AND CONCLUSIONS

The general pathologic and roentgen aspects of necrotic bone resulting from simple interruption of circulation and its repair are reviewed, and cases in which the lesion was produced by the trauma of fracture dislocation and operation are specially considered.

In the presence of fracture of the shaft there is more or less devitalization from injury of the circulation along the fragment ends. The necrotic bone undergoes creeping replacement by new bone and does not interfere with union of the fracture. In case of massive splinter formation or of extensive operative denudation of fragments there may be extensive necrosis of bone, which later undergoes creeping replacement similar to

the changes in a transplant. In some cases it may be a factor in the causation of nonunion.

Fractures bordering on joints in certain locations may result in extensive to complete severance of connections and necrosis of the bone of the articular fragment. This is oftenest seen in fractures of the neck of the femur, the carpal navicular bone and the condyles of the humerus. There is predisposition to nonunion by displacement and by interference with callus formation from the articular fragment.

The articular cartilage undergoes more or less nutritional disturbance, which contributes to the later development of arthritis deformans and osteocartilaginous loose bodies.

If the fracture does not unite, the dead bone is gradually invaded by blood vessels and fibrous tissue and is partially to completely absorbed and replaced by much less dense new bone.

If the fracture unites and the dead bone is protected from stress and strain, e. g., from weight bearing in case of fracture of the neck of the femur, it may be gradually replaced by new bone, and a fairly satisfactory functioning joint may be obtained. If there is too great stress and strain, the bone collapses, and the joint becomes deformed. In case of failure of complete substitution in the head of the femur, the remaining necrotic bone may become surrounded by a calcified fibrous capsule.

Dislocation of the hip may result in interruption of the blood supply and necrosis of the head of the femur. There may be subsequent collapse from weight bearing or creeping replacement by new bone, as in the case of united fractures of the neck of the femur.

The pathologic picture in a case of fracture-dislocation of the astragalus is reported, in which there were necrosis of both fragments and nonunion of the fracture.



# BUCCAL NEURALGIA

## A FORM OF ATYPICAL FACIAL NEURALGIA OF SYMPATHETIC ORIGIN

FREDERICK LEET REICHERT, M D  
SAN FRANCISCO

My reason for reporting on "buccal neuralgia" is that I have segregated a group of cases of a condition that falls into the general classification of atypical facial neuralgia but in which pain was limited to the cheek, upper jaw, malar region and nose. Moreover, a simple surgical procedure has been found that gave relief in a majority of these cases.

So-called atypical facial neuralgia is believed to originate in the sympathetic nervous system. Occasionally it is associated with "trigeminal tic douloureux," but it is not relieved by section of the sensory root of the fifth nerve. Atypical facial neuralgia is described as a deep-seated, dully aching, burning, throbbing, boring pain in the nasal, maxillary, zygomatic and temporal regions, in the jaw, in or behind the eye, in the nostril, in the cheek, in the gum and at times behind the ear extending to the occipital region and occasionally down the neck. The pain is not lancinating but tends to be constant, lasting for several minutes to hours or even days. It varies in intensity, and exacerbations of intense sharp pain may occur.

Sluder's, or sphenopalatine, neuralgia is described as pain in the root of the nose and in and about the eye, extending from the upper jaw to beneath the zygoma and back of the ear and frequently to the neck and shoulder. Some patients have been relieved by cocaineization or by injections into the sphenopalatine ganglion.

Vidian neuralgia is characterized by pain in the nose, face, eye, ear, head, neck and shoulder, occurring in severe attacks and relieved, as sphenopalatine neuralgia has been, by treating disease in the sphenoid sinus.

It will be noted that sphenopalatine and vidian neuralgia are similar to and belong in the group of atypical facial neuralgias.

These atypical facial neuralgias are differentiated from the tickle pains referable to the fifth and ninth nerves, which are stabbing lancinating, knifelike and momentary and which are readily induced by touch-

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From the Department of Surgery, Stanford University School of Medicine.

ing or moving the areas in the anatomic distribution of the trigeminal or the glossopharyngeal nerves

Sphenopalatine neuralgia was studied by Sluder<sup>1</sup> from 1908 to 1918 and remained as the chief neuralgia of the face other than true "trigeminal neuralgia" until Frazier and Russell,<sup>2</sup> in 1924, gave it the name of atypical facial neuralgia. They found over 100 cases of a condition that was not true "trigeminal neuralgia" and that failed to respond satisfactorily to any treatment.

Harris<sup>3</sup> in 1926 published his book on neuritis and neuralgia, which contained case histories of atypical facial neuralgia.

Fay<sup>4</sup> in 1927 called attention to the presence of tenderness to pressure over the carotid artery in the neck in cases of atypical facial neuralgia.

Frazier<sup>5</sup> in 1928 again discussed the unsuccessful treatment of atypical facial neuralgia by section of the various branches of the superior cervical sympathetic ganglion. Glaser<sup>6</sup> analyzed these cases of Frazier's, showing the similarity of symptoms, the lack of response to any treatment and the absence of any known cause. He divided them into ten groups, dependent on the location, extent and progression of the pain.

Peet<sup>7</sup> in 1929 expressed the belief that the pain of some of these atypical facial neuralgias originates in the sympathetic nervous system if due to vasomotor spasm, involving the sympathetic fibers on the external and internal carotid arteries.

It remained for Flothow<sup>8</sup> in 1930 and Mixter and White<sup>9</sup> in 1931 to report successful treatment of individual patients suffering from

1 Sluder, G. Headaches and Eye Disorders of Nasal Origin, St. Louis, C V Mosby Company, 1918.

2 Frazier, C H, and Russell, E C. Neuralgia of the Face. An Analysis of Seven Hundred and Fifty-Four Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, *Arch Neurol & Psychiat* **11** 557 (May) 1924.

3 Harris, W. Neuritis and Neuralgia, London, Oxford University Press, 1926.

4 Fay, T. Atypical Neuralgia, *Arch Neurol & Psychiat* **18** 309 (Aug) 1927.

5 Frazier, C H. Atypical Neuralgia. Unsuccessful Attempts to Relieve Patients by Operations on the Cervical Sympathetic System, *Arch Neurol & Psychiat* **19** 650 (April) 1928.

6 Glaser, M A. Atypical Neuralgia, So-Called. A Critical Analysis of One Hundred and Forty-Three Cases, *Arch Neurol & Psychiat* **20** 537 (Sept) 1928.

7 Peet, M M. The Rôle of the Sympathetic in the Atypical Neuralgias of the Face, *Arch Neurol & Psychiat* **22** 313 (Aug) 1929.

8 Flothow, P. Relief of Pain from a Neurologic Viewpoint, *Northwest Med.* **29** 69 (Feb) 1930.

9 Mixter, W J, and White, J C. Pain Pathways in the Sympathetic Nervous System. Clinical Evidence, *Arch Neurol & Psychiat* **25** 986 (May) 1931.

atypical facial neuralgia by interruption of the cervicothoracic sympathetic ganglions after section of the sensory root of the fifth nerve had given no relief

Migraine with associated phenomena referable to the sympathetic nervous system was successfully treated by Dandy<sup>10</sup> in 1931 and by Craig<sup>11</sup> in 1935 by "cervicothoracic sympathectomy"

Wilson<sup>12</sup> in 1932 believed that atypical neuralgia in some cases is psychogenic and advocated psychotherapy as the first treatment

Two interesting papers on the mechanism of the atypical facial neuralgias were published in 1932. Fay<sup>13</sup> expressed the opinion that the distribution of pain in cases of atypical facial neuralgia follows the arterial vascular tree of the neck and head. His observations were made on patients with the region under local anesthesia. Stimulation by faradic current of the bifurcation of the carotid artery was extremely painful to the patient. The sheath of the vagus nerve, composed of fine fibers arising from the carotid artery, was also extremely sensitive. By appropriate stimulation of points about the bifurcation pain may be referred into the tongue, into the jaws, into the face, about the orbit, into the temporal or the occipital area, deep into the eyes and head and into the throat. His case 9 showed that stimulation at the bifurcation caused pain to be referred into the malar region and the face, especially when the facial artery as well as the external carotid artery was tested. Stimulation of the internal carotid artery produced pain deep in the parietal area. The various combinations of nerve sections performed by Fay led to the distinct impression that the vascular "pain fibers" of the head and face enter the cranial nerves, particularly the vagus near the bifurcation of the carotid. A considerable portion of the fibers pass down along the vascular structures of the neck to enter the lower cervical and upper thoracic portions of the cord. By producing limited spinal anesthesia at the first thoracic segment of the cord Fay found that the atypical neuralgic pain to the malar region and tenderness to pressure on the carotid artery disappeared. "The deductions obtained from these tests indicate that the pain fibers from the face follow the carotid arteries, the internal and external jugular veins and other vascular

10 Dandy, W. E. Treatment of Hemicrania (Migraine) by Removal of the Inferior Cervical and First Thoracic Sympathetic Ganglion. *Bull. Johns Hopkins Hosp.* **48** 357 (June) 1931.

11 Craig, W. M. Hemicrania of Migraine. *Proc. Staff Meet., Mayo Clin.* **10** 362 (June 5) 1935.

12 Wilson, D. C. Atypical Facial Neuralgia. *I. A. M. A.* **99** 813 (Sept. 3) 1932.

13 Fay, T. Atypical Facial Neuralgia. A Syndrome of Vascular Pain. *Ann. Otol., Rhin. & Laryng.* **41** 1030 (Dec.) 1932.

structures and make their entry into the spinal cord in the upper three thoracic roots "

Davis and Pollock<sup>14</sup> in the same year presented evidence opposing the view of several observers that pain can be conducted antidromically over the anterior roots. These observers found that section of the posterior spinal roots and the fifth cranial nerve failed to produce complete analgesia, which then could be effected by sectioning the sympathetic chain. Davis and Pollock stated "On an anatomic basis the sympathetic supply to the structures of the face and head must be considered as consisting of purely efferent fibers." Using cats, they found that stimulation of the superior cervical sympathetic ganglion produced pain whether the trunk was intact or severed below the ganglion. Stimulation of the ganglion after section of the anterior or posterior spinal roots produced pain. Stimulation of the ganglion after section of the anterior spinal roots and the posterior root of the trigeminal nerve produced pain. But stimulation of the ganglion after section of the posterior spinal roots and the posterior root of the trigeminal nerve caused no pain. On an anatomic basis, the fibers from the superior cervical ganglion join the trigeminal nerve by way of the carotid plexus and are distributed through it to the structures of the head and face. To explain the failure to secure relief from the atypical facial neuralgia by cutting the trigeminal nerve root and the superior cervical ganglion, Davis and Pollock offered evidence previously obtained that sensibility to pain on deep pressure is transmitted by the seventh cranial nerve. Their explanation of their experiments was that stimulation of the superior cervical ganglion produces an effect that is carried by way of post-ganglionic efferent fibers to structures innervated by the sympathetic fibers. These efferent impulses produce an effect on the skin and other structures, so that possibly a metabolite is liberated which in turn stimulates the ordinary sensory endings of the trigeminal nerve. This impulse is transmitted centrally and recognized as pain.

In their paper of 1936, Davis and Pollock<sup>15</sup> again proposed to show that it is only the efferent fibers of the autonomic system itself which are concerned with the production of pain and that such afferent fibers as travel along with it belong to the ordinary spinal sensory system. In cases of pain in the face, the only proved contribution of the autonomic system to the production of the pain is in relation to referred pain, in which the efferent, not the afferent, fibers are utilized.

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14 Davis, L., and Pollock, L. J. The Rôle of the Sympathetic Nervous System in the Production of Pain in the Head, *Arch Neurol & Psychiat* **27** 282 (Feb) 1932

15 Davis, L., and Pollock, L. J. The Role of the Autonomic Nervous System in the Production of Pain, *J A M A* **106** 350 (Feb 1) 1936

Shaw,<sup>16</sup> in 1933, from clinical and experimental evidence, concluded that the sympathetic system possesses a sensory function and is concerned in the production of certain types of intractable neuralgia, since the residual sensation after division of the somatic innervation to an area of the body is dependent on fibers that traverse the ventral spinal roots, and these fibers are probably of sympathetic origin and pass through the anatomic sympathetic channels. This sensory residue is capable, Shaw found, of excitation by chemical stimuli of known sympathetic proclivity.

In 1934 I reported 5 cases of a combination of tic douloureux referable to the trifacial nerve and atypical facial neuralgia.<sup>17</sup> All the tic pains were relieved by interruption of appropriate branches of the trigeminal nerve, and 3 patients were relieved of the atypical neuralgia by alcoholic interruption of the cervicothoracic portion of the sympathetic chain.

Brickner and Riley<sup>18</sup> used the term autonomic faciocephalgia for atypical migraine and atypical facial neuralgia and reported 3 cases of atypical migraine relieved by epinephrine.

Harris<sup>19</sup> reported again in 1936 on ciliary or migrainous neuralgia in which the pain is especially located in, behind or around the eyeball. In his classification of fifteen varieties of unilateral pain in the head and face he divided the atypical facial neuralgias into four groups, which he called: 1 Migrainous neuralgia, an anterior migraine probably due to a vasomotor neurosis of the meningeal vessels, which may be cured by block of the gasserian ganglion or nerve block; 2 Sympathetic hemi-crania, with pain spreading to the back of the head and neck and associated with phenomena referable to the sympathetic nervous system. This may be relieved by intranasal spray of cocaine or by stellate ganglionectomy; 3 Chronic persistent neuralgia of the jaws, the temple and the side of the head and neck (Sluder's, sphenopalatine or vidian neuralgia), the algies sympathiques of the French writers, for which there is no treatment; 4 Facial psychalgia, clearly the result of a definite psychogenic factor and curable by psychotherapy.

In 1936 I described a form of atypical facial neuralgia about the teeth and cheek that was relieved by section of the facial artery, the vein

16 Shaw, R. C. Sympathetic System and Pain Phenomena. *Arch. Surg.* **27**: 1072 (Dec.) 1933.

17 Reichert, F. L. The Neuralgias of the Head and Face, *Am. J. M. Sc.* **187**: 362 (March) 1934.

18 Brickner, R. M., and Riley, H. A. Autonomic Facio-Cephalalgia, *Bull. Neurol. Inst. New York* **4**: 422 (Dec.) 1935.

19 Harris, W. Ciliary (Migrainous) Neuralgia and Its Treatment. *Brit. M. J.* **1**: 457 (March 7) 1936.

and the accompanying sympathetic fibers.<sup>20</sup> I also employed this procedure, together with division of all nerves and blood vessels beneath the eyebrow, to give relief in cases of supraorbital postherpetic neuralgia.

Glaser and Beerman<sup>21</sup> analyzed 200 cases of atypical facial neuralgia. In 47 per cent the pain started in the upper jaw, the malar region and the nose and spread from these areas to the head and neck.

Livingston<sup>22</sup> in 1938 found it difficult in the cases of patients with phantom limb pain to apply the theory that the relief of peripheral nerve pain obtained by section of sympathetic fiber tracts might be due to some alteration of the blood supply acting on pain receptors of the somatic nerves, since in his patients there were no sensory end organs in the parts where the pain was felt to originate.

Larsell<sup>23</sup> stimulated the nasal mucosa and observed the blood vessels in the ear of the rabbit after first sectioning the maxillary nerve proximal to the sphenopalatine branches. After section of the cord between the sixth and the seventh cervical segment or of the cervical portion of the sympathetic trunk, vasoconstriction did not take place when the stimulus was applied. His interpretation of the results confirmed the work of Davis and Pollock and others.

Tinel<sup>24</sup> reviewed the sympathetic neuralgias but could offer no relief for those involving the face. He felt that there is a "sympathetic afferent path" that is latent and only capable of being awakened in certain pathologic states to transmit severe pain.

Money,<sup>25</sup> using the classification of Harris, reported cures by injection of alcohol into the gasserian ganglion for migrainous or ciliary neuralgia and relief in cases of sympathetic hemicrania from "right stellate ganglionectomy."

Fay<sup>26</sup> divided pain into (1) the sharp, stabbing, shooting, lightning-like, cramplike momentary pain characteristic of true neuralgias, indicating intrinsic involvement of the nerve or its roots, (2) the burning,

20 Reichert, F. L. Treatment of the Neuralgias of the Head and Face, *Proc Second Cong Pan Pacific S. A.*, 1936, p. 183.

21 Glaser, M. A., and Beerman, H. M. Atypical Facial Neuralgia. An Analysis of Two Hundred Cases, *Arch Int Med* **61** 172 (Feb) 1938.

22 Livingston, W. K. Phantom Limb Pain. A Report of Ten Cases in Which It Was Treated by Injection of Procaine Hydrochloride near the Thoracic Sympathetic Ganglions, *Arch Surg* **37** 353 (Sept) 1938.

23 Larsell, O. The Sympathetics of the Head, *West. J. Surg* **46** 633 (Dec) 1938.

24 Tinel, J. Les algies sympathiques, *Arch internat de neurol* **57** 1 (Aug), 1 (Sept), 1 (Oct) 1938.

25 Money, R. A. Neuralgias of Cranial and Cervical Origin Other Than Tic Douloureux, *Australian & New Zealand J Surg* **8** 356 (April) 1939.

26 Fay, T. Problems of Pain Reference to the Extremities. Their Diagnosis and Treatment, *Am J Surg* **44** 52 (April) 1939.

scorching, tingling pain associated with causalgias, indicating compression, mild traumatic injury or constriction by adhesions along the nerve or its roots, and (3) dull, aching, throbbing, boring, pressure-like pain indicative of vascular pain and associated with some distention or stretch of the arterial and capillary network of vessels. He expressed preference for chordotomy of the anterolateral column for pain along the vascular pathway in the extremities but did not discuss the treatment of vascular pain in the face or head.

Thus, in the past thirty years attention has been kept focused on the unusual facial pains. The recent attempts to subdivide the large group of atypical facial neuralgias have permitted the development of therapeutic procedures that offer relief in a majority of cases. During the past fifteen years the autonomic nervous system has been implicated in these atypical facial neuralgias, and its role in the production of pain has led to important clinical and experimental observations.

#### BUCCAL NEURALGIA

Buccal neuralgia, a form of atypical facial neuralgia, is characterized by a burning, boring, aching, throbbing, toothachy pain in the region of the lip, cheek, gum, tongue, maxilla, nose, upper jaw and sometimes lower jaw, spreading at times to the zygoma, into or behind the eyeball or to the temporal region. It may be present for minutes to hours to days, with exacerbations of sharp, stabbing pain. Light touch to the involved part rarely starts an attack, but chewing, talking, local pressure or cold frequently induces an exacerbation. Hypersensitiveness to pressure over the carotid, facial and temporal vessels is frequently elicited. Extraction of teeth and injection of alcohol into the branches of the trigeminal nerve gave no relief. A few patients with hypothyroidism were relieved by thyroid extract and vitamin B. The majority of others were relieved by either alcoholic block of the cervicothoracic sympathetic ganglions or by resection at the lower border of the mandible of the facial artery, vein and sympathetic fibers.

#### ANATOMY

Not only were sympathetic fibers found on the facial artery and vein at operation, but from one to four rather large sympathetic fibers were resected in the soft structures surrounding these vessels (fig. 2).

Anatomic dissection of the sympathetic fibers in the face was rather difficult, but the semidiagrammatic drawing (fig. 1) shows the location and course of these fibers. To illustrate the numerous apparent anastomoses with the fibers of the seventh nerve in the cheek would be confusing, nor are the many small branches about the facial artery and vein indicated in the illustration. The main sympathetic fibers on

and accompanying the facial vessels course along the external carotid artery, where anastomoses are made with the fibers of the sympathetic trunk to the superior cervical ganglion and with fibers accompanying the temporal and occipital vessels, but the main group of fibers course downward to enter the carotid sinus at the bifurcation. The fibers from the carotid sinus pass downward along the great vessels of the neck to enter the cord at the seventh cervical and the first and second thoracic segments

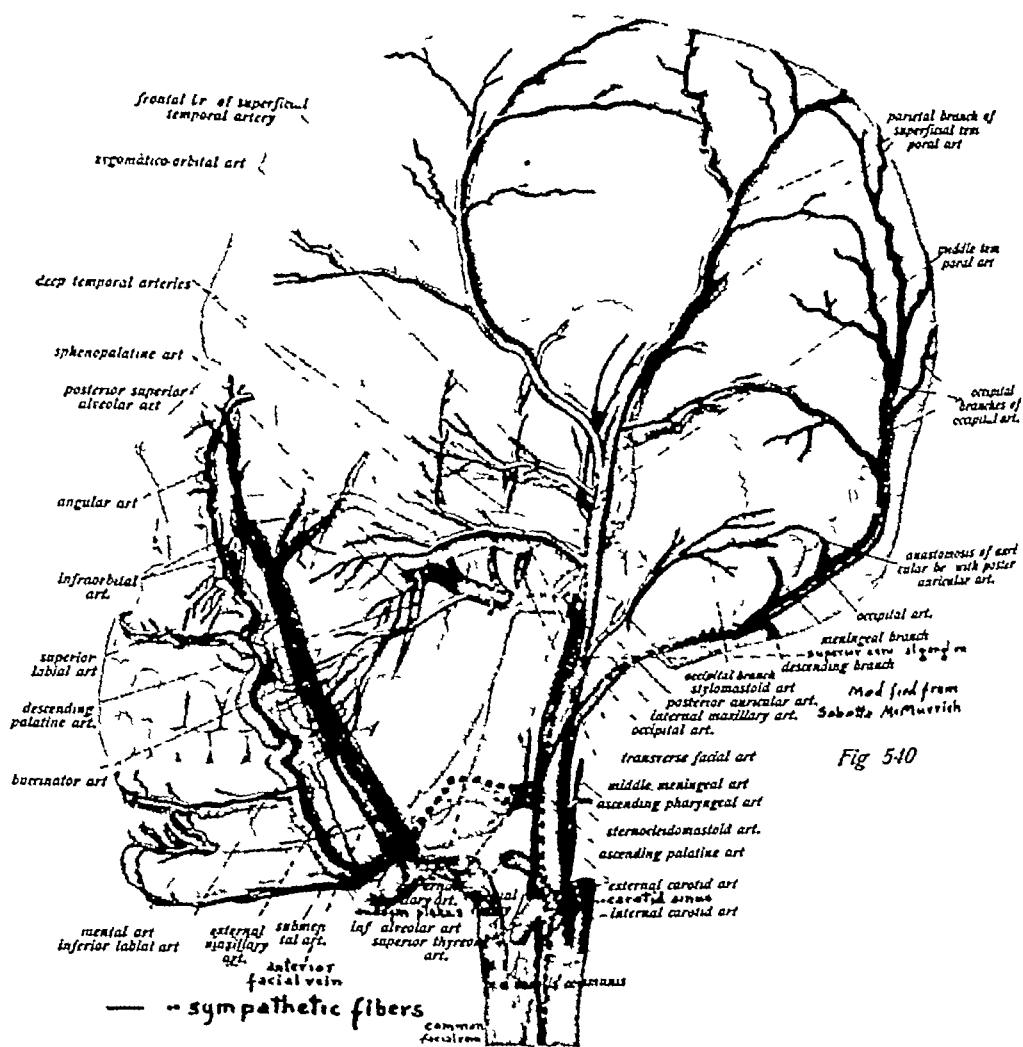


Fig 540

Fig 1—Semidiagrammatic representation from anatomic dissection of sympathetic fibers accompanying the arborizations of the facial artery and vein from the carotid sinus at the bifurcation of the common carotid artery (Modified from a drawing in Sobotta, J Atlas and Textbook of Human Anatomy, edited with additions by J P McMurrich, Philadelphia, W B Saunders Company, 1907, vol 3)

These anatomic findings on the course of the sympathetic fibers in the face seem to confirm the interesting experiments of Fay<sup>13</sup> when he stimulated (with the region under local anesthesia) the vascular tree in the neck of the human being



That the sympathetic fibers in the face are involved in buccal neuralgia seems evident from anatomic and clinical study, but no contribution has been made as to the mechanism of the pain. It was noted, however, in some patients that after resection of the sympathetic fibers accompanying the facial vessels an occasional pain was felt but gradually disappeared in from one or two days to three weeks.

#### TREATMENT

Surgical treatment for buccal neuralgia by dividing the facial vessels and the sympathetic fibers developed from the observations made in case 1 in 1929 and was first employed in 1932. Previously, in a majority of cases relief had been secured by the more difficult and extensive procedure of injection of alcohol into the cervicothoracic sympathetic ganglions<sup>27</sup>

The division of the sympathetic fibers along with the facial artery and vein is a simple procedure which does not produce Horner's syndrome or the troublesome alcoholic neuritis that appears after interruption of the cervicothoracic portion of the sympathetic chain.

With the region under local anesthesia an incision 2 to 3 cm long, parallel to and just below the lower border of the mandible, is made over the facial artery as it comes around the lower edge of the jaw (fig 2). A resection (with ligation) of 1 cm of the facial artery and facial vein, as well as of the contiguous soft parts containing sympathetic fibers, is made. The ends of the divided structures retract over the lower border of the jaw, preventing regeneration.

#### CLINICAL MATERIAL

Of the 30 patients seen during the past ten years that belong in the group classified as having buccal neuralgia, 1 patient, receiving no treatment, had spontaneous relief. Three other patients with hypothyroidism secured relief from administration of thyroid extract and vitamin B. Of 8 patients treated by alcoholic block of the cervicothoracic portion of the sympathetic chain, 5 were relieved at once of their neuralgia, 2 obtained no relief, and 1 had temporary relief. Division of the facial artery, vein and sympathetic fibers was performed in 17, and 13 were relieved of their neuralgia. Three were not helped by the operation, and questionable relief was secured in a "mental case." In 1 patient with limited buccal or angular neuralgia, relief was obtained by division of the angular artery, vein and sympathetic fibers. Ten patients had an associated tic douloureux of one or more branches of the trigeminal nerve.

<sup>27</sup> Flothow, P. G. Diagnostic and Therapeutic Injections of the Sympathetic Nerves, *Am J Surg* 14: 591 (Dec.) 1931.

## REPORT OF CASES

CASE 1—Mr O C M, aged 81, for twenty years had annual monthly attacks of burning pain, with frequent sharp stabs, in the right cheek and the lips, spreading to the zygomatic region. On examination, in February 1929, the right facial artery was tortuous and pulsated markedly. Its accidental occlusion by digital pressure at the angle of the jaw stopped the pain. When he returned, in October 1930, he stated that digital compression of this artery had given satisfactory relief during the last attack. No reply was received to a letter sent in January 1940.

CASE 2—Mrs H R, aged 27, had a burning, aching pain in the left side of the upper jaw and gum, spreading to the tongue and eye, which had been present for fifteen months. Cocainization of the sphenopalatine ganglion and injection of alcohol into the maxillary branch of the trigeminal nerve in April 1930 gave no relief. Her pain stopped spontaneously in September 1931.

CASE 3—Mrs S K, aged 58, had true tic douloureux of the left maxillary branch of the trigeminal nerve and a constant burning, aching pain in the left cheek, upper and lower jaw and the base of the tongue which were present for over a year. In April 1931 injection of alcohol into the lower two branches of the trigeminal nerve gave complete relief of the tic pain, but the burning, aching pain was not stopped until the sympathetic ganglions at the seventh cervical and the first and second thoracic segments were treated with injections of alcohol. It was reported that she remained well until her death in Japan in 1937.

CASE 4—Mrs M C, aged 48, underwent intracranial section of the right trigeminal root in September 1929 for tickle pains in the second and third branches of the nerve. In July 1931 she returned because of burning, scalding pain in the right cheek, tongue and lips, with aching in the zygomatic and maxillary regions. Injection of alcohol into the cervicothoracic portion of the sympathetic chain on the right gave relief up to the time of the last report, in February 1932.

CASE 5—Mrs G B, aged 27, with a toothachy pain in her left jaw and cheek spreading to her eye, was relieved in September 1931 by a paravertebral alcoholic block of the cervicothoracic sympathetic fibers. Neuralgia referable to the left geniculate ganglion developed in 1934. She reported in February 1940 that she had had no facial pain since treatment in 1931.

CASE 6—Mr A B, aged 40, suffered at intervals for fifteen years with tickle pains in the right side of the face, as well as a boring, aching pain in the right cheek, spreading to the eye and ear. Injection of alcohol into the right second branch of the fifth nerve in October 1931 gave relief until February 1932, when another injection was performed, but the boring, aching pain in the cheek persisted until relieved by injection of alcohol into the sympathetic chain at the seventh cervical and the first and second thoracic segments. This cervicothoracic portion of the sympathetic chain was removed surgically in September 1936, when the buccal neuralgia returned. Since then the patient has been free of buccal neuralgia, but reinjection into the maxillary branch was done in November 1939.

CASE 7—Mrs A R, aged 35, experienced neuralgia referable to the left geniculate ganglion, with aural herpes and palsy of the facial nerve in February 1930 followed by an attack on the right side with palsy of the nerve on that side in May 1930. These attacks left a residual pain, consisting of severe aching in the left cheek and in the jaws and ear. Injection of procaine hydrochloride into the left cervicothoracic sympathetic fibers gave temporary relief in September 1931 and again in November 1932. The patient died of uremia in January 1933.

CASE 8—Mrs M N, aged 52, in November 1931 complained of burning pain in the right cheek, tongue and zygoma, spreading to the eye. This was relieved by alcoholic block of the cervicothoracic sympathetic fibers on the right until February 1932. Elsewhere the trigeminal root was cut in 1937, and the facial vessels and sympathetic fibers were divided in 1938, without relief. She still suffers from buccal neuralgia.

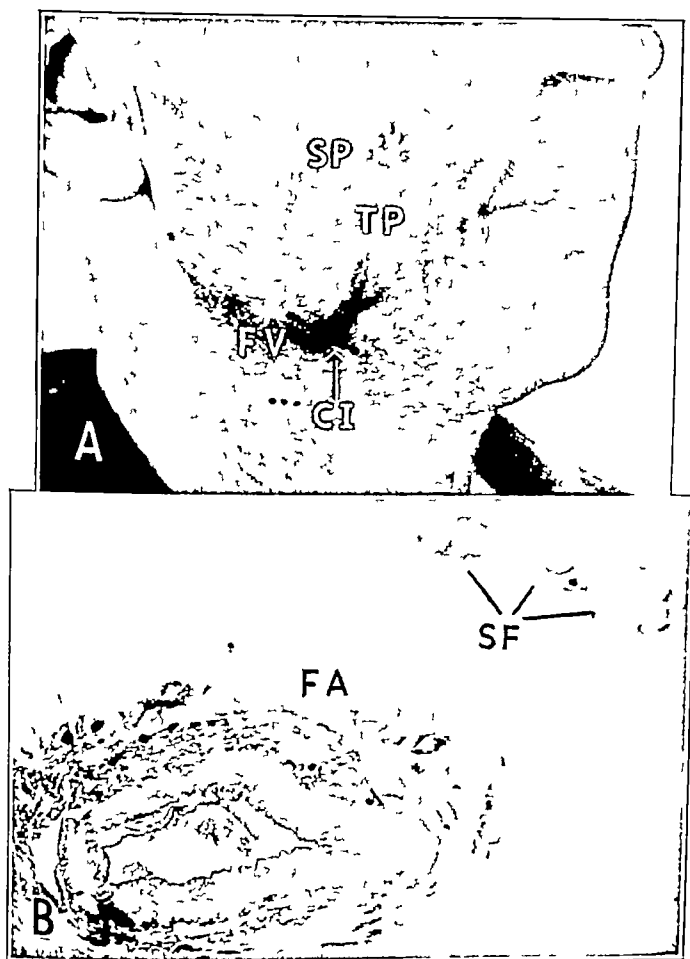


Fig 2 (case 9)—*A*, cutaneous incision indicated for division of the facial artery, vein and accompanying sympathetic fibers. *SP* represents stabbing pain, *TP*, trigger point, *FV*, facial vessels, and *CI*, cutaneous incision. *B*, photomicrograph showing many small sympathetic fibers in the tissue surrounding the wall of the facial artery as well as three larger sympathetic fibers in the tissue adjacent to the facial vessels. *SF* represents sympathetic fibers, *FA* facial artery.

CASE 9—Mr L W, aged 40, for over a year suffered from an aching throbbing pain in the region of the upper right first molar followed by a burning pain in the gum and upper jaw. Talking, eating and movement of the lips would induce the

attacks. Compression of the right facial artery immediately stopped the pain. In January 1932, with the region under local anesthesia, the facial artery, the vein and the accompanying sympathetic fibers were resected. Three large sympathetic fibers and numerous smaller ones in the loose tissue about the walls of the vein and artery were observed on histologic study (fig 2). An occasional stab of pain persisted for two weeks after operation. As recently as February 1940 an occasional stab would be experienced at weekly or bimonthly intervals.

CASE 10—Mr G W, aged 49, in May 1932 complained of a ticklike pain intermittently present on the right side for four years. Recently a burning, boring pain in the right upper jaw and cheek had developed. Alcoholic block of the right cervicothoracic sympathetic fibers in May 1932 and again in August 1935 cured the buccal neuralgia. On Feb 7, 1940, Horner's syndrome was still present, and a fourth injection of alcohol into the second and third branches of the trigeminal nerve was made to relieve the recurrent tic douloureux.

CASE 11—Mrs M B, aged 55, had the sensory root of the trigeminal nerve divided in 1930 by K McKenzie<sup>28</sup> for tic douloureux. Recent burning, crawling sensations in the left cheek and aching of the maxilla were only temporarily stopped by injection of alcohol into the cervicothoracic ganglions. In May 1933 excision of the left carotid sinus gave temporary relief. In February 1940 the pain was still present in spite of recent injections and operations on the sinus.

CASE 12—Mrs B E M, aged 65, had terrific burning pain over the left side of the forehead, in and behind the eye and along the cheek to the maxilla and nostril, following a supraorbital herpes zoster four months before. An incision through the left eyebrow, dividing all the nerves and blood vessels together with the sympathetic fibers and a second incision for division of the left facial artery, vein and sympathetic fibers gave complete relief of all pain except slight aching behind the eyeball. This relief extended from October 1935 until death in 1937.

CASE 13—Mrs E K, aged 62, underwent excision of the facial vessels and sympathetic fibers on the right in July 1936 for aching pain in the cheek and temporal region associated with attacks of stabbing pain in the same area. She has had no return of buccal neuralgia to date.

CASE 14—Mrs H L C, aged 67, had spells of burning, aching pain in the right cheek and nose, spreading to the eye and ear. When given thyroid extract and vitamin B in September 1936 she obtained relief within two weeks and had remained well to February 1940.

CASE 15—Mr F A B, aged 49, had frequent sharp pains in the upper left bicuspid for six years, associated with dull, aching pain in the left cheek, lip and nostril. In September 1936 the facial vessels and sympathetic fibers on the left were divided, with complete relief, which continued to the last report (October 1939).

CASE 16—Mrs G E H, aged 43, was seen in October 1936 for burning pain in the right cheek, jaw and nose associated with stabs of pain in the upper lip and nasolabial fold. She was found to have hypothyroidism. Thyroid extract and vitamin B gave relief until she stopped treatment, in the fall of 1939. Relief was again secured on resuming medication.

CASE 17—Mrs S E S, aged 62, suffered for four years from ticklike pain in left upper jaw and lip, as well as dull, aching pain in the left cheek and maxilla.

<sup>28</sup> McKenzie, K G. Observations on Results of Operative Treatment of Trigeminal Neuralgia, *Canad M A J* 29:492, 1933.

In October 1936 injection of alcohol into the maxillary branch cured the tic pain, but the buccal neuralgia persisted until resection of the facial vessels and sympathetic fibers. The last report, in February 1940, stated that she had remained free of buccal neuralgia since operation and from the tic pain since reinjection in February 1939.

CASE 18—Mr E C, aged 48, at intervals for twenty years experienced a constricting, aching pain in the left cheek, gums and upper teeth, spreading to the nose and behind the left eye. He has remained free of pain since division of the left facial vessels and sympathetic fibers in November 1936.

CASE 19—Mr F W W, aged 66, had ticlike pain in the left upper lip cured by injection of alcohol into the infraorbital nerve in February 1937, but a severe burning, aching pain in the left side of the face and upper lip was not relieved until the facial vessels and sympathetic fibers were divided a month later. Only a return of the tic pain was reported in February 1940.

CASE 20—Mr J M, aged 80, had a constant dull pain in the upper left gums and cheek which was not cured by injection of alcohol into the second and third branches of the trigeminal nerve and only temporarily relieved by division of the left facial vessels and sympathetic fibers in September 1937. He was committed to an institution because of disorientation and delusions of grandeur.

CASE 21—Mr J H R, aged 65, had a hammerlike pain in the left upper lip and upper jaw, extending to the tongue and cheek. Division of the facial vessels and sympathetic fibers in March 1937 gave relief until his death, in May 1939. In October 1937 a ticlike pain in the upper gums on the left was relieved by injection of alcohol into the maxillary branch.

CASE 22—Mrs A. J. M, aged 80, complained of a constant dull ache in the right angle of the mouth, spreading to the cheek and eye. A trigger point was found at the corner of the mouth. In January 1938 the facial vessels and sympathetic fibers were divided, affording temporary relief. She did not return for further treatment.

CASE 23—Mrs B T R, aged 46, had aching pain in the lower jaw, spreading to the left cheek and the zygoma for five years. Division of the facial vessels and sympathetic fibers in March 1938 and injections of procaine hydrochloride into the dental nerve and into the gums gave no relief, nor did thyroid extract and vitamin B.

CASE 24—Mr C E C, aged 43, has remained relieved of aching, burning pain in the left cheek and maxilla since division of the left facial vessels and sympathetic fibers in April 1938.

CASE 25—Mr A H, aged 62, had stabbing, throbbing, burning pain in the left cheek and jaws for five years. In April 1938 division of the facial vessels and sympathetic fibers on that side relieved the burning pain in the cheek, but the stabbing, throbbing pain persisted until alcoholic block of the mandibular branch of the fifth nerve. Return of the stabbing pain in August 1939 was relieved by reinjection into the mandibular branch.

CASE 26—Mrs E F, aged 62, had alcohol injected into the right maxillary nerve in April 1938 for stabbing pain in the right cheek. In January 1939 a burning, throbbing pain in the right cheek appeared which has not returned since division of the facial vessels and sympathetic fibers.

CASE 27—Mrs L C, aged 46, in January 1939 complained of nocturnal sharp aching pains in the right cheek, eye and upper jaw, which have been relieved by correcting her hypothyroidism with thyroid extract and vitamin B

CASE 28—Mrs M G D, aged 61, had attacks of burning pain in the left cheek, jaws and nose, spreading to the tongue. In March 1939 division of the facial vessels and sympathetic fibers on the left gave complete relief. There has been no report on the patient since April 1939.

CASE 29—Mrs H M, aged 57, suffered from attacks of aching, burning pain in the left cheek for sixteen years. Since division of the facial vessels and sympathetic fibers on that side in December 1939 she has experienced only an occasional pain in the cheek, with many intervening days when she is entirely free of pain.

CASE 30—Mr W E G, aged 59, had severe aching pain for a year in the left angle of the jaw seven years ago. Four years ago sharp pains followed by a burning, aching pain started in the inner angle of the lower left eyelid and extended down to the nasolabial fold and to the cheek. Injection of procaine hydrochloride into the infraorbital nerve gave no relief, but injection about the angular artery stopped all pain. In January 1940 excision of the left angular artery, vein and accompanying sympathetic fibers gave complete relief, which has continued to the last report (March 1940).

#### SUMMARY

Buccal neuralgia, a form of atypical facial neuralgia, is characterized by a burning, boring, aching, throbbing pain in the region of the lip, cheek, gum, tongue, maxilla, nose, upper jaw and sometimes lower jaw, spreading at times to the zygoma, into or behind the eyeball or into the temporal region.

Anatomic dissection demonstrated sympathetic fibers from the carotid sinus following the arborizations of the facial artery and vein.

Extraction of teeth and injection of alcohol into branches of the trigeminal nerve gave no relief.

A report is made of 30 patients suffering from buccal neuralgia.

Tic douloureux of one or more branches of the trigeminal nerve was associated with buccal neuralgia in 10 patients.

Three patients with buccal neuralgia exhibited hypothyroidism. The neuralgia was relieved by administration of thyroid extract and vitamin B.

Buccal neuralgia was cured in 5 of 8 patients in whom the cervico-thoracic portion of the sympathetic chain was interrupted.

Buccal neuralgia was relieved in 13 of 17 patients by the simpler procedure of division of the sympathetic fibers with the facial artery and vein at the lower border of the mandible.

# MICROSCOPIC CHANGES INDUCED IN THYROID GLAND BY ORAL ADMINISTRATION OF DESICCATED THYROID

USE OF THE SUBSTANCE IN TREATMENT OF CONGENITAL AND SIMPLE COLLOID GOITER

WILLIAM FRANCIS RIENHOFF JR., M D  
BALTIMORE

The first demonstration of the effect of a substance from outside the body on the microscopic structure of the thyroid gland was the deposition of colloid within the follicles of the thyroid gland of the dog after the administration of iodine, reported by des Ligneris<sup>1</sup> in 1907 and by Marine and his co-workers - in 1908. Since these early observations there have appeared in the literature from time to time controversial reports regarding the effects of iodine and other substances on the normal thyroid as well as on certain types of enlargement of the gland, (Loeb<sup>3</sup> and others<sup>3a</sup>). It would be aside from the purpose of this paper

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From the Department of Surgery, Johns Hopkins University

1 des Ligneris, M. Experimentelle Untersuchungen über die Wirkung des Jods auf die Hundesschilddrüse, sowie über die Hyperplasie dieser Drüse. Berne Rosch & Schatzmann, 1907

2 Marine, D, and Williams, W W. The Relation of Iodine to the Structure of the Thyroid Gland, Arch. Int. Med. **1** 349-384 (May) 1908

3 Loeb, L. The Structural Changes Which Take Place in the Thyroid Glands of Guinea Pigs During the Process of Compensatory Hypertrophy Under the Influence of Iodine Administration, Endocrinology **13** 49-62 (Jan-Feb) 1929

3a Webster and Chesney administered iodine in the form of compound solution of iodine U S P to 10 rabbits with hyperplastic goiters and observed rapid loss of weight, marked increase in heat production and death of the animal in most instances (Webster, B, and Chesney, A M. Endemic Goiter in Rabbits. III Effect of Administration of Iodine, Bull Johns Hopkins Hosp **43** 291-308 1928). They stated that "in every instance in which the animal survived the iodine administration for more than one week, a decrease in the size of the goiter was noted. Microscopic sections of the thyroid glands of the animals showed hyperplastic goiters in various stages of involution, and the degree of involution was directly proportional to the length of the period during which iodine was administered. The behavior of these animals suggested to the authors that after administration of iodine an excess of thyroid secretion had suddenly been elaborated and poured into the circulation. It was as if the thyroid glands in these animals had been

(Footnote continued on next page)

to attempt a critical resumé of the vast literature on this subject up to the present, for, although there have been many and important contributions to knowledge of enlargement of the thyroid gland, the cause and method of prevention of all types of goiter remain unsolved problems.

In all probability the goitrogenic factors vary in different parts of the world and particularly in various regions of the United States of America. Similarly, enlargement of the thyroid in certain localities will not only differ in extent but may show structural and microscopic changes varying from typical simple colloid goiter to goiter composed of small follicles which are poor in colloid. There will be found all gradations between these two distinct types, at times not only in the same locality but also in the same person. Again, such an enlargement may present as a diffuse or as a nodular goiter.

It would seem, therefore, that the methods of prevention of goiter as well as those of treatment would differ, depending on the locality, the extent of the enlargement and the microscopic structure of the gland. The deletion or inclusion of specific dietary substances effective in certain types of goiter under one group of conditions may be totally ineffective in another situation, in which a different type of goiter prevails.

The object of this report is to call attention to the therapeutic effect of desiccated thyroid in cases of simple colloid goiter of the type encountered along the mid-Atlantic seaboard and to note the effects of this substance on the microscopic structure of the gland. In the hope that some light may be thrown on atrophy of the thyroid, the accumulation of colloid in the gland and the entire complex subject of goiter, these data are presented.

#### REPORT OF CASES

CASES 1 and 2—In 1925 there appeared in the thyroid clinic of the Johns Hopkins Hospital dispensary 2 sisters aged 16 and 18, born in the United States of an American mother and a Swiss father. There was no instance of goiter on the maternal side of the family, but the father and the paternal grandparents were all affected with it. The 2 girls had been afflicted with large goiters since their birth in Baltimore, a nongoitrous area. They were, in addition, somewhat dwarfed compared with other girls of their age. Their facies and mental retardation

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rendered capable of synthesizing large amounts of thyroid secretion if the proper elements were available and did so as soon as iodine was supplied. In support of this view was the authors' observation that the severity of the reaction following the administration of iodine was proportional to the degree of hyperplasia present in the gland. Dr. Chesney, in a personal communication to me, has suggested that these hyperplastic thyroids might have elaborated a substance which was a precursor of thyroxin and that the administration of iodine served to convert this hypothetic substance into the active molecule, thus flooding the animal so to speak with an excess of the secretion of the thyroid gland.



dition were typical of a marked degree of hypothyroidism and in 1, the younger, immature congenital cataracts were present. Compound solution of iodine U S P in rather large doses (10 cc every day) had been given to both of them over a period in excess of two years, without beneficial results. On the contrary, there had in this time been a further enlargement of the thyroid. The basal metabolic rates on admission to the clinic were —26 per cent and —36 per cent respectively. For a number of months, while the iodine therapy was continued, these patients were kept under close supervision in the thyroid clinic. After repeated examinations, during which measurements were made of their enlarged thyroids, administration of iodine was stopped. In fact, not only did their clinical condition fail to improve as a result of administration of iodine, but the manifestations of hypothyroidism had become accentuated, and the goiters were increased not only in size, but in consistency. The increase in consistency produced an unpleasant sense of rigidity in the neck, especially when the patients lay in the recumbent posture.

On account of the low basal metabolic rates an attempt was made to relieve the marked functional deficiency of the thyroids by oral administration of tablets of desiccated thyroid. In a few weeks the dose was increased from 1 to 3 grains (0.06 to 0.19 Gm) per day, and as the basal metabolic rates mounted the thyroid glands began to diminish in size. After three months there was by actual measurement a return of the thyroids to almost the normal size, but there was still a considerable increase above normal in the consistency. After six months, during which 3 grains (0.19 Gm) of thyroid was given every day, there remained no visible evidence of goiter, and unless the rather pronounced induration of the thyroids was felt the abnormality in the glands would have remained unsuspected. The patients were clinically much improved, and their basal metabolic rates were restored to within normal limits. The younger was later successfully operated on by Dr Alan C Woods for bilateral cataracts, while the other was treated in the psychiatric outpatient department as an "intellectual inferior." After a few years they moved away, their destination unknown.

CASE 3—Some time later a newborn infant was admitted to the pediatric department of the Johns Hopkins Hospital suffering from severe dyspnea, cyanosis and a pronounced enlargement of the thyroid gland, present at birth. In view of our previous experience, thyroxin was given hypodermically, with very rapid amelioration of the respiratory difficulties and a demonstrable reduction in the size of the gland after a few days. The thyroid within some months was restored to a relatively normal size. Experience has demonstrated beyond question that in infants with such conditions iodine is totally inefficacious and surgical procedures very hazardous.

CASE 4—J L E, a boy 11 years of age, had diffuse goiter with hypothyroidism. The boy was also observed in the Harriet Lane Home in consultation with Dr Lawson Wilkins. The mother was operated on for an enlarged cystic thyroid gland slightly before the birth of this her only child. At the age of  $2\frac{1}{2}$  years a prominent enlargement of the thyroid gland developed, which increased in size each year. The attending pediatrician, Dr Robert Strong, concluded that the patient had a diffuse colloid goiter with hypothyroidism and gave the child iodine by mouth, which caused an increase in the size as well as in the consistency of the gland. The boy was then given 2 grains (0.13 Gm) of thyroid by mouth each day, with an early improvement not only in his mental status and alacrity but in his physical activities. At the time of this report the

thyroid therapy has been continued for nine years, during which time the child has developed mentally and physically in a normal manner. On occasions the thyroid has been temporarily discontinued. On all such occasions it is said the thyroid gland becomes much larger. He usually gains weight rapidly, at times as much as 11 pounds (5 Kg) in two months. He also becomes sluggish and irritable. The basal metabolic rate decreases rapidly, and the enlargement of the thyroid becomes more pronounced. In order to estimate the extent of his hypothyroidism all thyroid therapy was discontinued. In a few weeks the boy gained



Fig 1—A, J L E, showing the presence of a colloid goiter before oral administration of thyroid. B, semiprofile view. C, profile view. D, J L E after eight weeks of treatment with 3 grains (0.19 Gm) of thyroid per day. Compare with A. Note the disappearance of the goiter, due to atrophy of the thyroid gland. E, semiprofile view, compare with B. F, profile view, compare with C.

weight rapidly (8 pounds [3.6 Kg]), the abdomen became protuberant, and he became mentally sluggish as well as irritable. The thyroid gland increased in size each week. After two months the clinical manifestations of hypothyroidism were pronounced, and a marked enlargement of the thyroid gland was evident (fig 1, A, B and C). On palpation the gland was diffusely enlarged to about four or five times the normal size and much decreased in consistency. It was

similar in all clinical respects to a simple diffuse colloid goiter. The basal metabolic rate was — 18 per cent, and the value for blood cholesterol was 206 mg per hundred cubic centimeters. Three grains (0.19 Gm) of thyroid was then given by mouth each day, and in two months the physical status, the weight, the mental activities, the general briskness and the metabolic processes, *i. e.*, the basal metabolic rate and the level of blood cholesterol, had all returned to normal. Although the thyroid gland could be palpated, it was of normal size and consistency, more dense than before but much smaller. The fluctuations in size of the thyroid gland after discontinuance of the thyroid therapy with an interval, *i. e.* two months, before it was again administered were remarkable (fig 1, *D*, *E* and *F*).

CASE 5—In the fall of 1930 L. K., a married woman aged 30, was admitted to the Church Home and Infirmary complaining of goiter, choking sensations, difficulty in swallowing, shortness of breath, nervousness, poor appetite and loss of weight. The patient was born and reared in Thurmont, a few miles from Baltimore, in the flat, nonmountainous district of western Maryland. She had had an enlargement of her thyroid gland as far back as she could remember, but her general health had been excellent. The enlargement of the thyroid was a constant source of embarrassment to her. Her family and friends frequently made remarks concerning the gradual increase in the size of her goiter over a period of years. She had been married at the age of 24 and had one child. The size of her thyroid increased markedly during pregnancy and even more after her child was born. She had always felt sluggish, with practically no animation, and stated that her physician constantly told her that she had a very low blood pressure. Her hair, always dry, of late had been falling out. She was habitually slightly overweight, her eyes were somewhat puffy, and she had a tendency to gain weight even though her appetite was never good. Her pulse was usually slow. She had not been conscious of her heart beat. She rarely felt the heat and in the winter was cold almost constantly. Of late, however, she had become nervous about her goiter because, in spite of the fact that she had taken rather frequent and large doses of iodine in the form of compound solution of iodine U. S. P. by mouth for over two years, it was her impression that there had been no diminution in the size of her goiter but that, on the contrary, it had actually increased. She had estimated this increase by her own impression and by that of her friends and family as well as that of her family physician and also by the fact that she had experienced difficulty in breathing at times.

The patient was admitted to the hospital for examination and a study of the functional status of her thyroid gland. Physical examination gave essentially negative results except that the hair and skin were dry and the face somewhat puffy, particularly under the eyes. The subcutaneous tissue generally seemed to be thicker, as if there were some subcutaneous edema. There were no signs of hyperthyroidism. On inspection the thyroid gland was obviously enlarged to several times its normal size. This enlargement on palpation was revealed to be diffuse. The gland was soft. There were no nodules or tumors. The consistency of the parenchyma seemed to be definitely decreased below that of a normal thyroid gland. The impression obtained from examining this patient was unquestionably that of hypothyroidism resulting from or associated with diffuse soft colloid goiter. The basal metabolic rate was — 10 per cent.

This patient was admitted for operative removal of a portion of the enlarged thyroid gland because medicinal (iodine) therapy had been totally ineffective. The thyroid gland under this form of therapy had increased not only in size but in consistency and was productive of more mechanical disturbance in this

hardened state than before the iodine was given. The question immediately arose as to what could be expected of further iodine therapy, whereupon it was generally agreed that the colloid already present in the gland under this form of treatment would probably become more dense and that more colloid would be deposited as a result of the administration of iodine. The possibility of intoxication due to the prolonged use of iodine must always be held in mind. In addition to this, the patient had lost her confidence in the probability that the iodine would bring about a reduction in size of the gland. An operative procedure to remove the enlarged gland for cosmetic reasons seemed illogical in the presence of the low basal metabolic rate already present, together with clinical signs of underactivity of the thyroid or of hypothyroidism. It was felt that further destruction of the thyroid gland would only increase the hypothyroidism and lead to additional untoward clinical manifestations. It was therefore decided to treat the patient by means of oral administration of thyroid tablets (Hynson, Westcott and Dunning), beginning with 1 grain (0.06 Gm.) a day and increasing the dose according to the condition of the patient and the changes noted in the basal metabolic rate. Before this type of therapy was instituted the matter was discussed thoroughly with the patient, and with her complete approval as well as understanding removal of a biopsy specimen from the thyroid with the region under local anaesthesia was decided on in order to determine the exact histologic characteristics of the gland. The patient had not taken iodine in any form for approximately six months before admission to the hospital, so it was felt that any effects of the iodine on the structure of the thyroid or on the organism as a whole would in a large measure, if not entirely, have disappeared. Accordingly, a small portion of the right lobe was removed for section. The thyroid gland in the gross seemed to be of uniform consistency, and the diagnosis of diffuse colloid goiter was unquestionably correct. The section of the gland taken before treatment with thyroid was studied and showed typical diffuse colloid goiter (figs 2 and 3). A description of several sections of the tissue removed at the first biopsy follows. The histologic appearance was that of a simple colloid goiter. The follicles were everywhere filled with homogeneously staining colloid. The follicles differed in size but were, generally speaking, much larger than those seen in the normal human thyroid. The colloid abutted on the epithelium, which had been flattened out to almost the size of endothelial cells, much lower than the normal cubical epithelium usually encountered throughout the thyroid of the normal person. In places, even in this section, the pyknotic nuclei stood out in the cytoplasm like pearls in a necklace, the cytoplasm of the lining epithelium being apparently made scanty by increased intrafollicular pressure of the colloid. In some areas the epithelial cells could not be distinguished from the endothelial cells except for their position as a part of the lining of the follicle, their nuclei being flattened and the cytoplasm merely tapering off from this elliptic type of nucleus. Practically no secretion vacuoles were seen in the lumens of the follicles. The smaller ones, between the larger, in all probability represented terminal portions of follicles of equal size which had been sectioned at different levels and which if they had been reconstructed would in all probability have been as large as the average in the section. The largest follicles seemed to have been cut across through their diameters. Except for blood vessels and lymphatics there was practically no interfollicular tissue. There were no wandering cells, lymphocytic cells or small mononuclears. Occasional clumps of cells, which obviously were epithelial and represented the domes of the underlying follicles, could be observed between those follicles which contained colloid. The microscopic appearance of this section was therefore typical of a simple colloid goiter, with accumulation

of colloid in large distended follicles lined with an atrophic type of epithelium, the latter, in all probability, being produced in part by pressure atrophy. The microscopic appearance of the cells was everywhere one of relative inactivity, and from the histologic appearance there seemed to be an accumulation of secre-

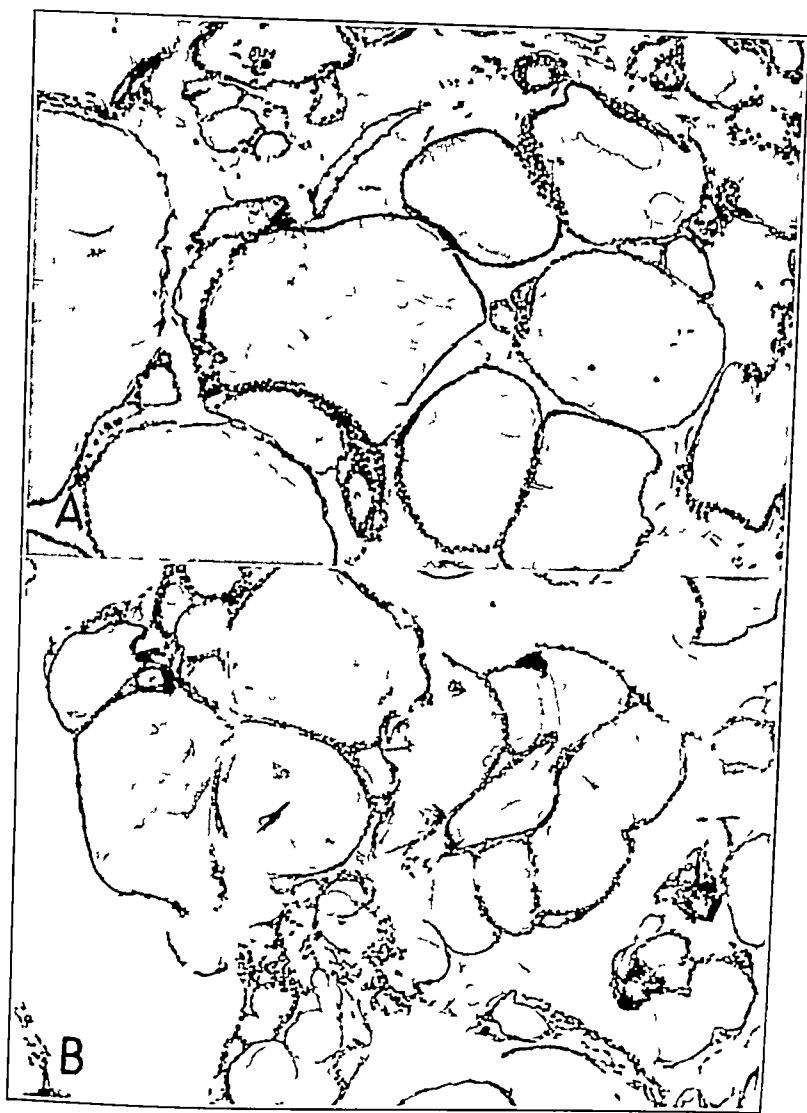


Fig 2—*A*, photomicrograph of a section showing typical simple colloid goiter ( $\times 100$ , hematoxylin and eosin stain). The tissue was removed from the gland before oral administration of thyroid was instituted. Note the size of the follicles and the characteristics of the lining epithelium and the interstitial tissue. *B* section (hematoxylin and eosin  $\times 100$ ) of tissue removed for the first biopsy as was that in *A*, but from another portion of the block.

tion, namely, the colloid, resulting from inability of this substance to escape into the blood stream. In other words, it appears that the gland, owing to its inadequate excretion, was ballooned out by its own secretion.

The patient was then given thyroid tablets (1 grain, or 0.06 Gm) by mouth for one week. The dose was increased from 1 grain a day in the first to 2 grains (0.13 Gm) a day in the second week, 3 grains (0.19 Gm) a day in the second month, and up to 4 grains (0.26 Gm) a day for the remaining four months of a six month period. This was increased by the patient on her own initiative to 6 grains (0.39 Gm) a day for six months. It is to be noted that thyroid was administered first in October 1935. She returned April 15, 1936, at which time her basal metabolic rate had risen from -10 per cent to +11 per cent. During this period she had been taking 4 grains (0.26 Gm) of thyroid a day. She had lost considerable weight and was feeling much better, and the gland had decreased

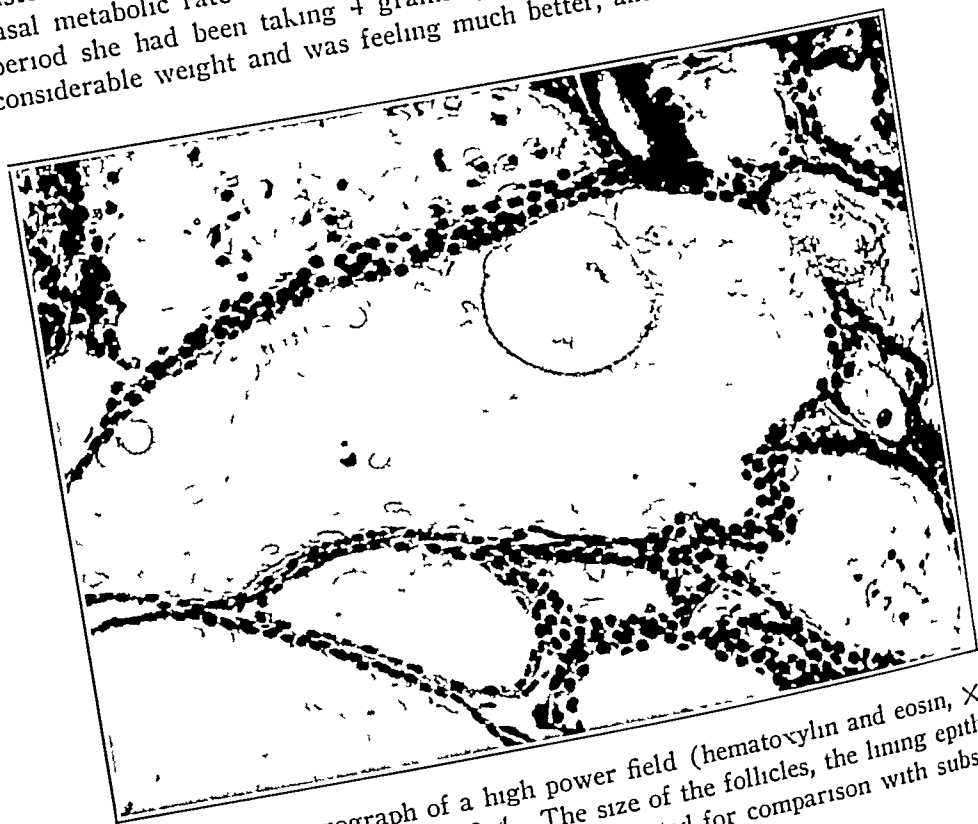


Fig 3—Photomicrograph of a high power field (hematoxylin and eosin,  $\times 200$ ) from the section shown in figure 2 A. The size of the follicles, the lining epithelium and the paucity of interstitial tissue are to be noted for comparison with subsequent figures.

markedly in size. She was mentally more alert, and her skin was somewhat oily and seemed to be of a finer texture. The falling out of her hair had ceased, and clinically she appeared to have distinctly less hypothyroidism.

It is interesting to note that during the first four or five months the patient stated that she was nervous, had palpitation and noticed some shortness of breath and increased fatigability. Later, although without seeking advice, she increased the dose of thyroid to 6 grains (0.39 Gm) per day, after which the disagreeable symptoms of an excess of thyroxin in the circulating blood and tissues, *i. e.*, nervousness, insomnia, palpitation, premature systoles, a sense of increased tremor and loss of weight, were not as prominent as when she had taken a smaller dose of thyroid, *i. e.*, 3 to 4 grains (0.19 to 0.26 Gm) per day. She had evidently established a tolerance for thyroid, and it had become less effective.

We have noted this tendency before and have felt that it is due not only to tolerance on the part of the patient but to atrophy of the thyroid gland with diminution of its secretion in the circulating blood caused by the exogenous supply of thyroid

The patient then returned to her home, where she remained until Sept 2, 1936, after taking thyroid in large doses for practically one year. At the end of this time she was readmitted to the Church Home and Infirmary, feeling much better than she had on the previous admission, although she was taking 6 grains (0.39 Gm) of thyroid each day. She stated that she "felt her heart beat" somewhat more rapidly than before she had begun to take thyroid, but less so in the last four months. She was vigorous, did not sleep so much and on the whole felt that her condition had improved. She seemed to have a great deal more energy. The most striking feature was complete disappearance of the enlargement of the thyroid gland, or goiter. This was noticed by the same group of persons who had commented on the goiter previously, namely, her family, friends and family physician. Measurements of the neck made at the first and at this second admission also confirmed this observation. Examination at this time revealed a rather rapid pulse rate (running from 100 to 110), a perfectly regular pulse, an occasional premature systole, a well defined tremor of the extended fingers and a definite severity of expression, probably due to a retraction of the upper eyelids and a suggestive superior lid lag on rotation of the bulbs downward. The most interesting part of the examination centered around the thyroid gland. At this time the gland was not visible, the goiter had entirely disappeared. On palpation there was a small shrunken thyroid, markedly hardened and increased in consistency, entirely different to palpation from what it had been originally. In fact, it felt almost stony hard, like beginning Riedel's struma, and markedly diminished in size. It was as small as a normal gland, which corresponds to a diminution at least to one-fifth its pretherapeutic size. The basal metabolic rate at this examination was + 25 per cent, which was a total advance of 35 above the - 10 per cent noted on the patient's first admission to the hospital. On account of this marked elevation of the basal metabolic rate, which I thought was due to the hyperthyroidism induced by the patient's taking 6 grains (0.39 Gm) of thyroid a day, and on account of the marked shrinking and hardening of the gland, another biopsy specimen was taken from a representative portion of the thyroid definitely removed from the previous incision so that the microscopic appearance would not be interfered with by scar tissue from the previous removal. A small piece of tissue was thus removed, and photomicrographs of this are presented (figs 4 and 5).

There was marked diminution in the number and size of the follicles (compare with figure 2A), and there was also a paucity of colloid. That which was present stained homogeneously but somewhat deeply with eosin. One gained the impression that the colloid secretion remaining in the small and atrophic follicles was desiccated and hard. The great majority of the follicles were entirely empty or contained only a very small amount of colloid. They were decreased in size and number while the intrafollicular stroma was everywhere strikingly increased. In some regions there appeared to be a large amount of substitution of fibrous tissue for parenchyma, giving the appearance of areas of broad scar formation. In other places there was a pronounced infiltration of small lymphocytic cells which in some areas formed what appeared to be actual germinal centers similar to those described by MacCallum<sup>4</sup> as observed in the thyroid glands of patients with

4 MacCallum, W. G. The Pathology of Exophthalmic Goiter. J. A. M. A. 49:1158-1162 (Oct 5) 1907.



Fig 4—*A*, photomicrograph (hematoxylin and eosin,  $\times 100$ ) of tissue removed from the thyroid gland for the second biopsy, after oral administration of thyroid for one year. Compare with figures 2 and 3 (same patient). The thyroid parenchyma has undergone pronounced atrophy. Note the diminution in size and number of follicles and the apparent increase in interfollicular fibrous tissue, together with the infiltration of small lymphocytes. Germinal centers (originally described by MacCallum) are seen at the lower portion of the section. For complete description, see text. *B*, photomicrograph (hematoxylin and eosin,  $\times 100$ ) of a section from a different portion of the same block. The follicles are small, the majority are empty, and the colloid present is desiccated. There is infiltration with small lymphocytes. The epithelial cells are clear except for pyknotic nuclei. The eosin-staining protein content of the cytoplasm seems to have disappeared.





Fig 5—*A*, high power photomicrograph (hematoxylin and eosin  $\times 200$ ) of the section shown in figure 4 *B*, demonstrating more clearly the empty follicles and the clear cytoplasm of the epithelial cells. The photomicrograph also shows that the interfollicular stroma is to a large extent composed of masses or cords of epithelial cells derived from the collapsed, empty follicles. *B*, high power photomicrograph (hematoxylin and eosin  $\times 200$ ) of a section of the same block shown in figure 4 and in *A*, demonstrating the contracture of the follicles to very small vesicles or even to such an extent that their lumens are obliterated so that the appearance of the section is that of a solid cord of epithelial cells.

exophthalmic goiter It is interesting to note that in this instance also the patient, being stimulated by oral administration of thyroid, was in a state of clinical hyperthyroidism Although there were many clusters of epithelial cells, which seemed to adhere to no particular pattern, the follicles which could be made out clearly were markedly reduced in size, containing a desiccated-appearing colloid or (as in the majority of instances) seeming to be entirely empty They were lined with epithelium which consisted of very low cuboidal cells, the cytoplasm of which was almost colorless or took only a faint eosin stain The protein content of the cells seemed to be much diminished, in some there was a cytoplasm that was atrophic but took a pink eosin stain fairly well The nuclei were shrunken and pyknotic in the majority of cells and were irregular in shape, in some they were perfectly flat like endothelial cells No secretory vacuoles were noted. There were entire areas of epithelial cells which stood out mainly by virtue of the nature of the pyknotic nuclei These cells appeared as empty spaces surrounded by a thread-like wall In some areas these cells were radially arranged, often with their apices touching and in such close contact that no lumen in them could be seen They merely made up cordons of atrophic epithelial cells and generally created the appearance of a large increase in the interfollicular stroma In other places, rather large follicles in which the lining cells were absolutely colorless predominated The lining cells looked almost like foam cells There was generally an infiltration of the stroma with small lymphocytes around and between the large and empty follicles Unless one had observed very closely the impression might have been obtained that there were large areas of scar formation, but these were made up in the main by small follicles from which the colloid had been absorbed and which, as a result, had shrunk down to become an almost solid cord of perfectly colorless cells In other places there apparently was a definite increase, at least a relative one, in the pink-staining (eosin) white fibrous connective tissue The gland had everywhere the appearance of disuse atrophy with the colloid secretion markedly decreased, that which was present before the excretory demands were so lowered (owing to the exogenous thyroid) had been absorbed On account of the oral administration of thyroid the parenchyma of the gland had undergone true disuse atrophy rather than destruction of tissue The areas that seemed to be scar may have been due merely to shrinking of the parenchyma, that is, the absence of colloid-containing follicles between normally placed and normal-sized fibrous connective tissue septums The last-mentioned structures, owing to the relative shrinkage of the follicles, stood out much more prominently

On account of the elevation of the basal metabolic rate and the clinical suggestion, particularly the ocular signs, of slight but definite hyperthyroidism, together with the microscopic appearance of atrophy of the thyroid gland, the patient was discharged to return and was told to discontinue all medicinal therapy No thyroid or iodine in any form was administered, and particular attention was paid to the table and cooking salt to be sure that no iodized salt was ingested

The patient remained away from the hospital for four months During this period her nervousness entirely disappeared, as the thyroid had been discontinued On her readmission to the hospital, although she seemed perfectly normal from the standpoint of her history and physical condition, the basal metabolic rate had dropped to —15 per cent on Jan. 18 and to —4 per cent on Jan. 25, 1937 The thyroid gland was apparently enlarged and felt a great deal softer than on the previous admission This decrease in consistency was thought to be due to the colloid reaccumulating rather rapidly in the gland

Another biopsy was performed in order to determine the histologic status of the gland at this time, when the influence of oral administration of thyroid had

been discontinued Typical sections from the gland at that time are shown in figures 6 and 7

The most extraordinary histologic transformation had occurred after discontinuance of the feeding of thyroid by mouth The follicles were everywhere filled with homogeneously staining colloid, and except for a few, between which the intrafollicular septums had ruptured, were slightly larger than those encountered in the normal gland The colloid seemed fresh in appearance, and where the follicle was distended abutted on the epithelium or was prevented from doing so by an accumulation of chromophobic vacuoles The follicles were everywhere spherical, lined with active epithelium which varied from high cuboidal to columnar The nuclei were less pyknotic and much more nearly spherical, and in some nucleoli were evident The cytoplasm of the cells was plentiful and took a pink stain diffusely throughout the cytoplasm, except for areas in which there seemed to be accumulations of chromophobic vacuoles and chromophilic granules The appearance of the follicles was entirely different from that in previous sections In some areas the epithelium was actually comparable with that which occurs in cases of hyperthyroidism, in that there were marked hypertrophy and hyperplasia and signs of pronounced cellular activity The interfollicular material was markedly reduced, there being little except a few endothelium-lined, flattened capillaries and some relatively inconsequential amounts of white fibrous tissue which probably represented the normal septums of the gland The areas of dense lymphocytic infiltration with germinal centers could no longer be observed The gland had the appearance of marked activity as a result of withdrawal of oral thyroid therapy and throwing of the gland on its own resources The secretory mechanism seemed to be functioning efficiently and rapidly The cellular constituents of the parenchyma were in an active physiologic state as far as one could tell from the histologic appearance The follicles, ballooned up to their previous size, were filled to their utmost capacity with homogeneously staining colloid, which first distended and then compressed the interfollicular tissue and accumulations of cells, thus creating the appearance of a marked reduction in the stroma A general estimation of the number of follicles per field in this section taken four months after discontinuance of thyroid therapy, gave one the impression that no actual loss of tissue had occurred during the atrophic resting state but that the follicles were merely collapsed and shrunken because they were drained of all their colloid through gradual absorption or excretion The threshold stimulus for the gland to secrete was never reached on account of the artificial feeding of thyroid After this had been discontinued for four months the stimulus for the gland to secrete was again present and this was met by marked increase in the cellular activity, thus colloid was deposited as was shown in the final section, which represented practically a reversion to the primary stage of simple colloid goiter Evidently this state of hypersecretion together with hypertrophy and hyperplasia of the epithelium preceded the formation of a colloid goiter at least in this instance and in all probability in others It thus may be that a state of secretory activity may always precede a colloid goiter and it would seem also to be a matter of fact that when there is not sufficient threshold stimulus for the gland it will undergo atrophy followed by hypertrophy and hyperplasia when that stimulus is restored to normal

This change in the histologic appearance of the gland was interesting, and instructive, for it seemed to indicate that the thyroid was on its way back to its previous state and was going through a period of hypertrophy hyperplasia and

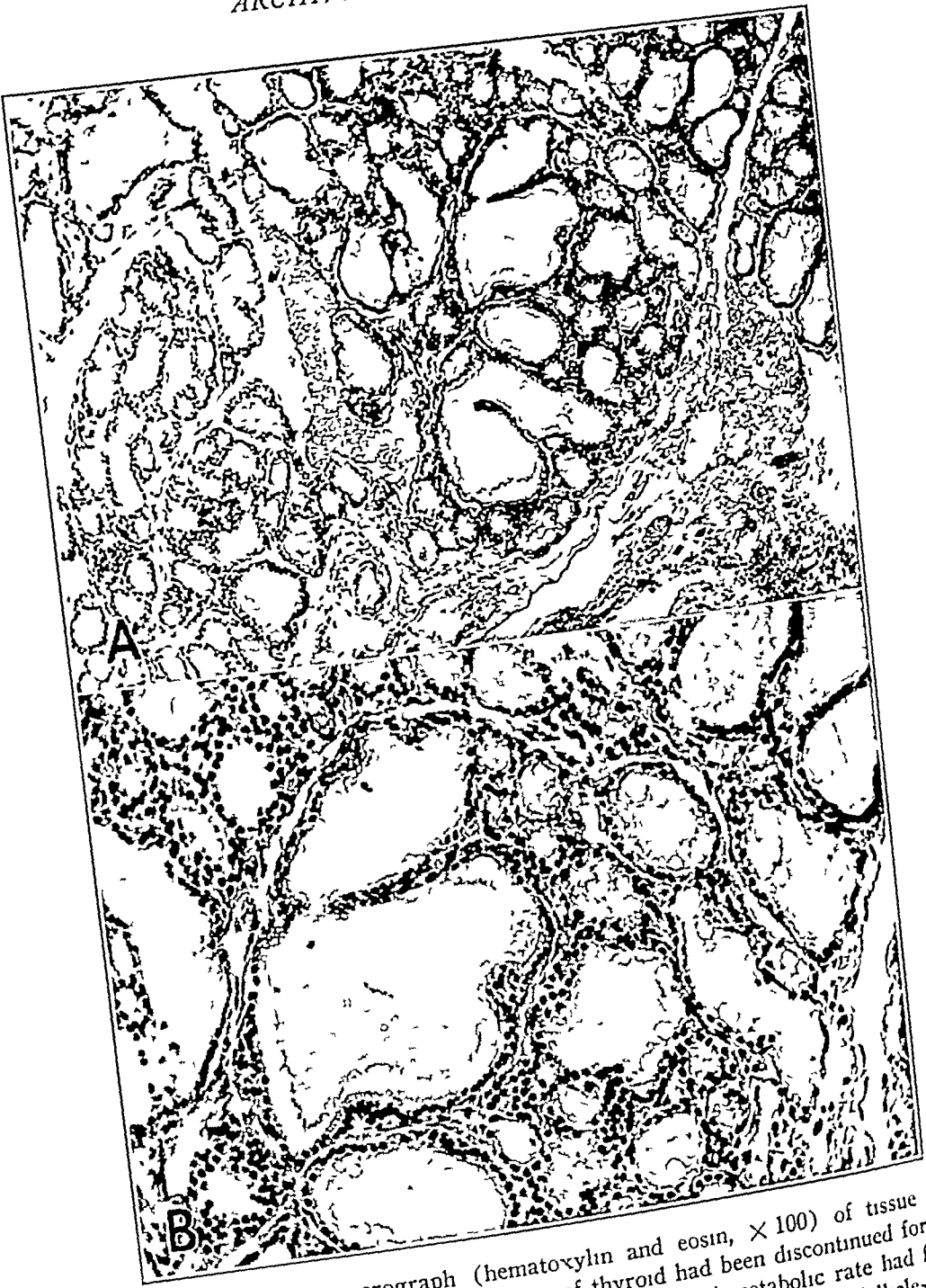


Fig 6—*A*, photomicrograph (hematoxylin and eosin,  $\times 100$ ) of tissue from the same patient after oral administration of thyroid had been discontinued for four months. The thyroid gland was enlarged, and the basal metabolic rate had fallen. The follicles were beginning to fill with colloid, the epithelial lining follicles were active and in many places were columnar. Secretory vacuoles were present. The follicular stroma was much diminished by filling of the follicles, part of the stroma having been composed of collapsed follicles giving the appearance of cords of epithelial cells. Distention of the follicles had also displaced and compressed the interfollicular septums and the blood vessels. Generally the follicles were smaller than those in figures 2 and 3, and their process of refilling was probably only partially accomplished. *B*, high power photomicrograph (hematoxylin and eosin,  $\times 200$ ) of the same section. Note the secretory vacuoles and the hypertrophy and hyperplasia of the epithelium.

secretory hyperactivity due to the fact that the body demanded secretion of the gland (which during the recent atrophic stage had been supplied by the oral administration of thyroid)

It is to be noted here that during this stay in the hospital the basal metabolic rate was recorded on two occasions as  $-15$  and  $-4$  per cent, respectively, and

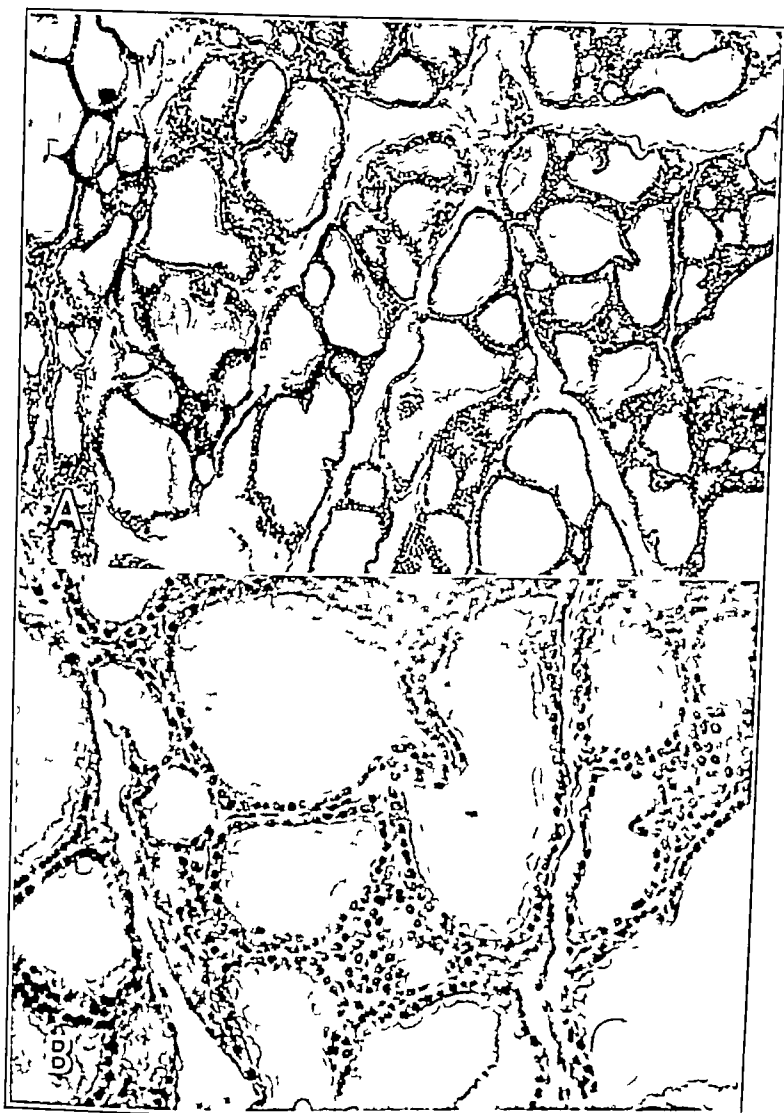


Fig 7—*A*, photomicrograph (hematoxylin and eosin  $\times 100$ ) showing epithelial hyperactivity with the refilling of the follicles with colloid *B* high power photomicrograph (hematoxylin and eosin  $\times 200$ ) of the same section. Note the refilling of the follicles with colloid and the epithelial hyperplasia. Figures 6 and 7 are to be compared with figures 4 and 5.

yet the histologic appearance of the thyroid was that of pronounced cellular activity, i. e., hypertrophy and hyperplasia. This suggests that in this instance, at least, colloid goiter may have been preceded by a period of histologic activity not only from the state of a normal gland but even from that of an atrophic thyroid. In order to determine this point it was decided to let the patient go without any further thyroid by mouth for another three months. This was perhaps a stage of hyperactivity on the part of the gland that precedes the stage of inactivity or lessened activity associated with increase of colloid and inability of the gland to excrete its secretion. Accordingly, the patient was discharged from the hospital, and in three months she was readmitted for a fourth biopsy. Thus, the period without thyroid by mouth was seven months. The patient had gone back into her original state of hypothyroidism. The thyroid gland, although not

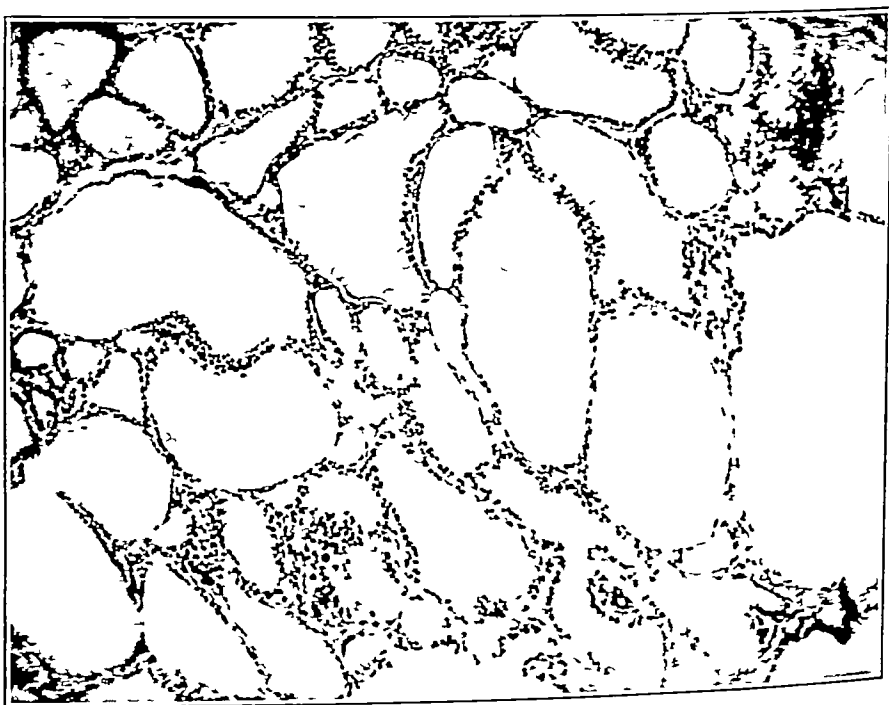


Fig 8—Photomicrograph (hematoxylin and eosin,  $\times 100$ ) of a biopsy specimen from a patient six months after oral administration of thyroid was discontinued. The follicles are larger than normal, the epithelium returning completely to the resting, inactive state. This occurred simultaneously with the clinical signs and symptoms of hypothyroidism and redevelopment of colloid goiter.

quite as large as at first, was prominent and, except for the two small scarred areas, was essentially as soft as before. The basal metabolic rate at this time was  $-13$  per cent. Biopsy revealed a complete revision to the previous state of histologic inactivity (fig 8).

The patient was then discharged from the hospital and directed to take 2 grains (0.13 Gm.) of thyroid a day. She has been taking that amount since April 1927. In the interval she has remained perfectly well. Her signs of hypothyroidism have disappeared, her thyroid gland cannot be seen, and it is felt with difficulty. Five grains of thyroid seems to be just the right amount to overcome her natural

deficiency, and at the same time it permits sufficient atrophy of the gland to accomplish a favorable cosmetic effect and do away with the goiter

In July 1936, in the Johns Hopkins Hospital, with the permission of Dr Dean Lewis, Dr Fred W Geib, the resident surgeon, repeated for corroboration the observations described Three biopsies were performed on a patient with diffuse colloid goiter before and during the oral administration of thyroid The details of this case are as follows

CASE 6—A W, a white boy aged 15 years, was admitted to the surgical service on May 28, 1935 The clinical diagnosis at this time was diffuse colloid goiter with hypothyroidism At the age of 11 years this patient had noticed that his neck had begun to enlarge, and for four years the increase had been continuous In the last year he had taken iodine pills frequently and had rubbed 'iodine salve' on the skin of his neck over the goiter During this period the increase in size of the gland had been accelerated, and it had become much harder (This is the usual history obtained from patients taking iodine over long periods)

Examination of the patient at this time revealed a fat boy, rather sluggish, with puffy features There was a large, collar-like mass in the neck which on palpation was very soft The pulse was slow, and the patient presented the clinical picture of diffuse goiter with hypothyroidism The basal metabolic rate was  $-11$  per cent.

Biopsy of a specimen from the thyroid at this time revealed typical diffuse colloid goiter

In the outpatient department the patient was given 1 grain (0.06 Gm) of thyroid each day, and by June the basal metabolic rate had risen to  $+15$  per cent, a total of 25 points In July 1935 the oral dose of thyroid was elevated to 1 grain (0.06 Gm) twice a day, and by July 23 the basal metabolic rate had fallen to  $-2$  per cent. This decrease in the basal metabolic rate occurred in spite of an increase in the amount of thyroid the patient was receiving by mouth Simultaneously the thyroid gland had become much smaller and harder The patient continued to take 3 grains (0.19 Gm) of desiccated gland by mouth for ten months, at the end of which time he was readmitted for biopsy (April 4 1936) At this time the thyroid was reduced even more in size, so much, in fact, that no sign of a goiter was present The remaining gland was very hard and had obviously undergone pronounced atrophy The basal metabolic rate on this admission was  $+4$  per cent The general condition of the patient, both physically and mentally, had vastly improved. Biopsy at this time supported the clinical impression that there was atrophy of the thyroid gland The microscopic appearance was characteristic of the diffuse atrophy observed in the previous case and shown in figures 10 to 13 The patient was again discharged from the hospital and advised to discontinue taking thyroid by mouth. He returned in four months when a section of his thyroid gland revealed a reaccumulation of colloid such as occurred in case 1 (figs 6 and 7)

Since that time a number of patients with large diffuse and soft nodular colloid goiters associated with a low basal metabolic rate have been successfully treated by oral administration of thyroid in increasing doses over a considerable period—a number of months In all the goiter has been reduced, if not completely to the size of a normal thyroid, so

effectively that the patients were completely satisfied from a cosmetic standpoint. The restoration of their metabolism to within normal limits has resulted in a pronounced improvement not only in their physical appearance but in their mental reactions.

#### COMMENT

From the clinical as well as the microscopic standpoint, atrophy of the thyroid gland has been produced by oral administration of tablets of desiccated thyroid. The extent of the atrophy as well as the permanence depends on the size of the dose. As the thyroid of the recipient becomes more and more reduced in size and function, ever increasing doses of thyroid must be administered to maintain the same degree of hyperthyroidism. In spite of the possibility of developing antihormones, the explanation of the latter observation may well be found in the gradual diminution of secretion of the patient's own thyroid due to disuse atrophy of the gland and requiring additional amounts of thyroid by mouth. This same tendency has been noted during administration of solution of parathyroid as well as of insulin. It may be stated as a biologic law that organs whose function is no longer necessary go into a regressive state, and it would appear to be applicable to the endocrine glands. The function of such glands is in all probability regulated by the concentration of their secretion in the blood or tissues. When the glandular secretion in the blood stream is consumed, a temporary response on the part of the gland is produced, with a proportional mobilization of its secretion. A typical example is the mobilization of the hepatic sugar and the level of blood sugar. The thyroid secretion in the blood stream probably determines the degree of activity of the thyroid parenchyma at any given time. Thus the cellular activity of the thyroid gland would take place at a minimum rate in the presence of an abundance of exogenic thyroid in the blood stream. The changes observed in the histologic structure of the thyroid described here would seem to bear out such a hypothesis.

It is a conjecture, but not beyond the realm of probability, that in forms of enlargement of the thyroid other than simple colloid goiter, atrophy may be accomplished in a similar manner. It is even possible to conceive that the diffuse hypertrophy and hyperplasia associated with hyperthyroidism could be brought under control to an atrophic state, and this interesting problem is being investigated at present. In order to produce such a change in the gland a slightly larger amount of thyroid must be administered artificially than is sufficient to equal the rate of secretion of the thyroid gland. As the size of the gland diminishes and the consistency gradually increases the amount of exogenous th



may be reduced proportionately until the minimal requirements have been determined. It will probably prove necessary to produce at least a mild degree of relative hyperthyroidism in cases of the colloid type of goiter before definite atrophic change in the thyroid will be brought about. The degree will possibly vary with the patient, according to age and the size of the gland. Another variable factor will undoubtedly be the period necessary for administration of thyroid by mouth. It is to be noted, however, that in patients afflicted with nodular or diffuse colloid goiter there is a coexistent state of clinical hypothyroidism. Soon after thyroid medication is begun there is a striking improvement symptomatically, and the further development of low grade hyperthyroidism is so insidious that the patient is unaware of any unpleasant effects of the increased thyroid medication. On the same principle, thyroid in small doses, 1 to 2 grains (0.06 to 0.13 Gm.) per day, has been administered by mouth to patients recovering from operation (double partial lobectomy) for hyperthyroidism. In these cases the sudden fall of the level of thyroxin in the blood stream is broken, and at the same time the brunt of the demand which originally caused hypertrophy and hyperplasia of the gland to occur is satisfied largely, if not entirely, by the thyroid artificially supplied. The glandular tissue remaining after operation is in this manner given an opportunity to quiet down and pass into an inactive state histologically. Thyroid medication has been discontinued by gradually diminishing the dose over a period of three weeks. Further periods of administration of thyroid may be employed in the future if there is a tendency to recurrence of the hyperthyroidism or if hypothyroidism persists.

It may prove after further experience and investigation that another type of diffuse goiter with hyperthyroidism might be benefited by oral administration of thyroid, that is, the so-called "iodine-fast thyroid," in which the follicles are filled with colloid after administration of iodine but in which clinical hyperthyroidism has recurred after escape from an artificial iodine remission. Further remission cannot be obtained in this type of gland, because successive colloid tamponades cannot be induced by prolonged administration of iodine. Gradual absorption of the deposited colloid associated with atrophy or diminished function of the thyroid should, even if complete atrophy cannot be accomplished, at least permit an efficacious colloid tamponade after resumption of iodine therapy. Exogenous thyroid, by resting the hyperplastic gland, enables it to absorb the entrapped colloid. As things now stand patients with this condition are denied proper preoperative preparation, and they afford a relatively poor surgical risk.

The fate of the colloid in the transition from a colloid goiter in which the follicles are bulging with colloid to the atrophic stage in which the acini are essentially empty and shrunken is a matter of conjecture. The epithelial cells may absorb it, or the larger part may be excreted from the follicle, after which, the demand of the body having been removed, there is temporary cessation of epithelial secretion. The small amount of colloid present seems to be inspissated. The clear cytoplasm of the epithelial cells in the atrophic stage would also suggest that, secretion having ceased, the follicle once emptied by discharging its contents had not been refilled. The depletion of colloid might suggest that active secretion of the thyroid is chemically bound to it rather than held merely by adsorption, in which latter case the colloid, acting as a mere vehicle, would remain after consumption of the secretion.

The histologic appearance of the stage of atrophy, if observed without knowledge of the microscopic appearance before and after the onset of this stage, would give the impression of a chronic inflammatory process associated with diffuse and pronounced destruction of the parenchyma of the thyroid. The apparent fibrosis, the atrophic follicles, which in many fields appear as cordons of epithelial cells without a lumen, the dense desiccated colloid, and the pronounced infiltration of the parenchyma with small lymphocytes, even forming germinal centers, in many ways corresponds with the histologic appearance of struma lymphomatosa of Hashimoto. It will be recalled that the last-mentioned condition is supposed to be a forerunner of Riedel's struma. The microscopic appearance of the thyroid in cases of cortical atrophy of the adrenal in which there is atrophy of the thyroid histologically with marked infiltration of the lymphocytes is similar to that described here.

MacCallum<sup>4</sup> called attention years ago to the infiltration of the struma of the thyroid gland with small lymphocytes in patients suffering with hyperthyroidism. It is thus interesting that in the patient in whom an artificial hyperthyroidism has been produced the thyroid, though atrophic, is everywhere invaded with these cells, the concentration in certain areas simulating germinal centers. After administration of thyroid by mouth has been discontinued and hyperthyroidism has subsided, biopsy reveals that the lymphocytes have disappeared entirely from the gland. It may be that the thyroid secretion has a stimulating effect on the thymus.

From the sequence of changes noted in the microscopic structure of the thyroid gland following oral administration of desiccated thyroid, it seems possible that the mechanism of secretion of the thyroid cells might continue to function even hyperactively, but the mechanism for discharge

of this secretion into the blood stream may, for unknown reasons, fail. As a result, storage of an excess amount of colloid in the follicles would occur. Secondary pressure effects, such as ballooning of the follicles and pressure on the follicular septums with flattening of the lining epithelium, would follow, resulting in the histologic appearance of simple colloid goiter.

One point would seem very likely, *i. e.*, that two separate functions are fulfilled by the follicular epithelium, one the manufacture or secretion of thyroxin and the other the release of thyroxin into the blood. Interference with the balance of the usually smoothly functioning mechanism will produce extensive histologic changes within the gland and physiologic disturbances in the organism as a whole.

## OPINIONS ON THE APPENDIX AFTER THIRTY-FOUR YEARS

M W ROAN, M D

BISMARCK, N D

This article has been written purposely in a style that is entirely foreign to the usual scientific publication, which follows a strict cut and dried pattern, stating the problem with its history, experimental and clinical notes and discussion, then closing the article with conclusions. Probably the main reason that this discourse does not follow the usual routine is because it is believed this will be enjoyed by Dean Lewis, who in his prime, endowed with that gift of the warmest human relationship, always maintained his students' utmost interest by striving for something new, different from the ordinary and entirely free from dullness. Although this article may seem to lack the genius of Dean Lewis and contains nothing startling, it no doubt expresses the opinions of many general surgeons. Further, it may bring out many truths not to be found in much of the literature on this most common of surgical conditions. It is believed that even in the most formal medical journals an occasional publication of this type will be welcomed by the physician.

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"The appendix should be removed at the earliest possible convenience."

Most surgeons become more convinced of the truth of this statement with each year of their experience and wonder why there was ever created a small, wormlike rudimentary hollow tube at the beginning of the large intestine in practically every mammalian. At times it seems its sole purpose is to cause pain, suffering and death, and at the same time to give the surgeon the opportunity to do some of his most noble work. Yet in spite of surgeons' most noble efforts and study with marked modern scientific advancements, the appendix, in the role of the most common and most prevalent major surgical problem, still brings to persons of any age a dangerous and treacherous condition. This ominous, degenerate small organ, as it has done in the past, continues to pay many a young surgeon's bills and brings him into the lap of luxury in some instances, a fact of which most surgeons are well aware, nevertheless, in most instances the surgeon's recompense, no matter how great, cannot match the service he is rendering the patient by removal of this structure.

After thirty-four years of general surgical practice, in which approximately 2,500 appendixes have been removed and during which the many statistical and scientific accounts in medical journals from various sections of the country have been appraised, medical and surgical cl

attended and the medical and surgical fads mixed with real scientific progress observed, one cannot help acquiring a definite philosophy on the appendix, some of which has already been expressed

Every community, from the rural settlement to the largest metropolis, is made up of persons who are all capable of having "bellyaches" and as such are all candidates for possible trouble with the appendix. Educating them to regard with concern the common "bellyache" has done much to bring these persons to the physician early. In spite of this, instinct seems to tell many that to move the bowel will relieve the pain, while others procrastinate with the ice bag and remedies "of great and low degree," and after failure of these finally see the physician. Avoidance of laxatives and of procrastination is the only salvation for the person with an angry or poorly behaved appendix. A crusade against these two factors seems to be the main point of attack to reduce the entirely too high mortality rate from disease of this degenerate organ.

Because of laxatives and procrastination, together with individual peculiarities of development and reactions as varied as people themselves, the surgeon has to be prepared for almost any type and condition of appendix when he begins his search. Most surgeons may have a good idea of what they will find and how, why, where and when they will find it before they operate, but there is not a surgeon living today, nor has there been one, no matter how great (except the Great Healer) nor is it believed there will ever be one who can foretell the findings each time before the abdomen is opened. Even after opening of the abdomen, on some occasions great surgeons have been baffled. But once the appendix is found and identified as the culprit (and even when it appears innocuous but no other criminal is identified), two problems remain, namely, what technic shall be employed in the handling of this degenerate and what after-care shall be given the rest of the body to which the appendix is doing or may do harm.

Diagnostic methods, surgical technic and treatment including that following operation, are well taught to the present student in the approved medical school and internship. Logic explains that practically every surgeon and physician wishes to see his patients do well, and to this end he will strive to develop the best methods and technic possible. He will try to improve and adapt to his own peculiarities and best abilities that which he has learned from school, internships, clinics, journals and probably most of all, his experiences. Consequently, surgical methods and after-care and treatment, although in most instances similar, show minor differences almost as varied as the surgeons themselves with the end results of the conscientious ones practically the same. One occasionally wonders why two surgeons in opposite corners of the continent employing different methods and techniques and having somewhat

different ideas, manage to get the same end results in their honest statistical columns, while each using the other's method would meet with disaster. Possibly this may be explained by the fact that each surgeon has learned to know his abilities, his shortcomings, what he can accomplish and dare try or do, together with the fact that he knows his community and its people and has developed his own special methods and technic.

Technic and method of dealing with the appendix in Bismarck, N D., are presented in the following story in résumé of a thirty-four year period. Probably all over the United States surgeons have encountered identical or slightly varying experiences, the story of which might read similarly to this one.

Impressed with my training in the clinics of J B Murphy, A J Ochsner and my other instructors, I set out in surgical practice in this small western community. Still fresh in my memory and ringing in my ears were some of the words of advice and wisdom of these great surgeons—words and truths that have stuck with me and proved their worth for thirty-four years.

"Pain without fever—appendicitis. Fever without pain—typhoid."

"Sudden or acute abdominal pain—appendicitis until proved otherwise. Always give the patient the benefit of the doubt."

"There is no argument whether a patient has appendicitis or not—remove the appendix."

"Pain, nausea, tenderness, then temperature."

"There is no honor in removing a ruptured, gangrenous appendix, it should have been removed before it ruptured."

With these and many other maxims I began my surgical activities. It did not take long to find that the majority of my surgical cases, as they have continued to be, were cases of appendicitis. Much to my sorrow, a large percentage of the patients were not seen early, as they had frequently been in the Chicago clinics, but instead came in by buggy and train from points hundreds of miles away, with abdominal conditions days or weeks old. Appendical abscesses and perforated gangrenous appendixes seemed more frequent than I had ever thought they would be. Schools and teaching clinics were not located in communities where their patients had so many miles to travel and where some education of the public had taught them not to rely on home remedies for "bellyaches." I soon found myself draining many appendical abscesses. Once the abscess was drained, the patient received the Murphy drip per rectum and hypodermoclysis with standard saline solution (physiologic solution of sodium chloride was not used in Bismarck then), managing to obtain what appeared to be an adequate fluid intake otherwise than by the oral route. Plenty of morphine seemed not to

to make these patients more comfortable but to hasten their convalescence, as it has continually proved to do. Most of my patients, sometimes surprisingly even to me, although draining unbelievable amounts of foul pus, got well. I then wasted no time in explaining to them that with their recovery they should be sure to return and have the appendix removed in the near future. That was a different matter, for once a human being is feeling well the future seems to be forgotten. I waited, but many did not return as advised, and frequently those who did were forced to do so because once again they had an appendical abscess. Once again I could only drain the abscess and impress on them that this time they must return to avoid a similar experience.

Gradually I began to wonder why some of these patients with appendical abscesses could not have their appendixes removed at once, since frequently they failed to return as directed. Consequently, just before the United States entered the World War I began to remove more and more appendixes, taking the greatest care not to spread the infection or break down nature's resistive barriers. I found that my mortality rate did not increase. From that time on I removed more and more appendixes. Thus it has not been necessary for the patient to return, and the end results have been apparently as good as previously. I have read the numerous fine reports of surgeons who have decreased their mortality rates by postponing operation in certain select cases, parenteral fluids, morphine and conservative measures being used until masses in the right side have subsided. In this western community I have hesitated to do this (although occasionally there is a case in which I postpone operation), and in comparison my mortality figures seem favorable, with the advantage that the patient has the appendix removed without the risk of a later surgical procedure. My best end results are obtained by removing the offending organ when possible and as soon as possible after a diagnosis of some type of appendical disturbance has been made. It goes without saying that after traveling miles many of the patients are tired, cold and in mild shock, and for these it has been found desirable to wait, frequently as long as eight hours, until they are rested or the shock is relieved, before submitting them to operation.

In the diagnosis of appendicitis I have found that a carefully taken history and a careful physical examination are usually all that is necessary. In the early days I did not have the benefits of blood counts, differential counts and "shifts to the left," but I soon learned not always to depend on the blood count. Often the patient's history alone was worth a dozen blood counts. Helpful as laboratory procedures have been, they are not to be trusted explicitly at any time and with them as with other diagnostic methods, I have failed as does every one to make the correct diagnosis in some cases. With time it has become

apparent to me that, although one may have a good idea of what is present in the region of the appendix, one cannot be absolutely sure of the diagnosis and findings until one gets into the abdomen, and even then sometimes one fails to find the proper solution of the problem.

In my early cases in which drainage was required I found that even with the McBurney type of incision a postoperative hernia would occasionally occur. It occurred to me that if I made this incision farther over to the side there would be less abdominal pressure and consequently possibly less chance of herniation. As the appendix is usually opposite the anterior superior spine, I began making my incisions much closer to this and toward the side, usually about 1 inch (2.5 cm) from this palpable prominence. Not only did this type of incision seem to afford an easy approach and better drainage, but it did away with herniations. Through the years I have considered this type of incision the one of choice. I have found that a large incision is not necessary, but this one can be enlarged without difficulty. When I cannot accomplish through this incision all that is desired, I have always remembered that this incision can be quickly closed and a new approach made through a right rectus or a midline incision, remembering that these other types of incisions are apt to increase morbidity. Once through the skin and external fascia, the external oblique muscle is incised in the same diagonal approach. The wound is retracted toward the midline, and once again exactly opposite the anterior spine a nick is made in the aponeurosis of the internal oblique muscle. I usually tell my assistants that they should have no trouble finding this point, for the point of incision is labeled by the fibers making a V which points toward the anterior superior spine. A forceps is then placed in this incised nick, and the fibers are spread down to the peritoneum, which is picked up, and the abdominal cavity is opened. In closing the abdomen two continuous sutures in this aponeurosis are usually adequate.

During my student days it was of interest to me to note how long it took some surgeons to find the appendix. It seemed to be right under their fingers, and I often wondered why they did not just pull it out. I decided early to try to develop a definite method whereby I would not have to feel so long for the appendix, realizing that use of sight greatly aids the search. This early decision brought out the fact that by beginning opposite the anterior superior spine and guiding my fingers posteriorly along the parietal peritoneum toward the midline I usually encountered a fold of the peritoneum holding the cecum or appendix (not the mesoappendix), and by hooking my fingers under this and pulling gently upward and toward the wound I frequently brought the appendix into view. Many of my assistants have learned to use this method, and, although it is known that it does not work in every case,



it seems to be worth while in the majority of cases, so that a prolonged search is not necessary. Every new assistant I have is told of this method and is advised to look in the anatomy books for this "appendical ligament," which he usually does, returning with skepticism but soon saying, "It sure works and saves time hunting for the appendix."

It has always been necessary for me to buy my own catgut in the community and local hospitals. I soon found that with a satisfactory technic it was not necessary to use more than one tube of catgut for the whole appendectomy, silk being used for the skin. My assistants soon find that it is not necessary to use more than one tube of plain catgut. Lately I have watched some of my assistants use silk and have noted articles favoring silk over catgut, but after thirty-four years I am in no hurry to change.

For plain acute appendicitis, clamping and cauterizing with phenol neutralized with alcohol has seemed to serve me well, the stump being tied and inverted in a purse-string suture. After the purse-string suture is tied the strings are left long and placed around the mesoappendix, and it is ligated and its clamped forceps released, this being brought directly over the cecal area of the appendix. Occasionally this cannot be accomplished, and a separate tie around the mesoappendix becomes necessary, but this has worked out well in the majority of my cases. When I have had the opportunity to inspect this later it has presented a smooth area, free from any adherence to the abdominal peritoneum. For the gangrenous appendix, for the ruptured appendix and in cases in which a purse-string did not seem advisable I merely tied off the severed appendical stump. I found that occasionally fecal fistulas were occurring. To avoid this I developed a method of putting a few sutures in the severed stump of the appendix, usually above the clamped forceps, and then tying the stump below this suturing, which was also tied. After this, fecal fistulas became a rarity, but how this was accomplished and why I do not know.

The matter of drains was always of interest to me. I have carefully watched the numerous articles on drains, including their uses and abuses. I admire surgeons who get excellent results in closing abdomens that I would perhaps drain, yet I feel that my end results are comparable, with just as few adhesions and not much longer periods of hospitalization. I have noted the many articles proving that the peritoneal cavity cannot be drained and that it is foolish to try to drain it, still I like to see drains go into the abdomen when I feel it is necessary. I like to use the common Penrose rubber drain. At one time I found that occasional subphrenic or pelvic abscesses were following "purulent appendectomies." To avoid these abscesses I began putting down one drain toward the pelvis and one toward the liver besides the third down to

the appendical stump in the "purulent cases" Since then I have used three drains in this manner. Students fresh from internships, assisting me, have wondered if I was not spreading pus by placing the drains in this manner. They found to their surprise, as I had known they would, that the patients got well without pelvic and subphrenic abscesses and when followed in after years did not seem to be troubled with adhesions.

After the war I introduced dextrose solution into Bismarck for the first time. This seemed to be of considerable benefit for patients requiring drainage, but I still dread to think of the chills that used to occur. I marvel now at the intravenous solutions available and the ease of giving adequate parenteral fluids. In fact, because of this ease I have cautioned my helpers against too much of the electrolytes.

There are many more things that could be mentioned in this story of the appendix, such as stomach tubes with modern suction bottles for distention, positions of the patient, hot abdominal packs, blood transfusions, the use of oxygen and many more factors, down to the use of modern chemotherapy.

I know that my methods and technic would perhaps not work as well for other physicians in other communities as they have for me. Likewise, I am certain that the methods of others would not work so well for me.

I have always been convinced that the important work of the surgeon is not the spectacular procedure lasting a few minutes in the operating room but the careful, tedious and painstaking preoperative and postoperative care. As a result of this conviction few of my patients with appendicitis die, and the majority go home without further trouble so far as the appendix is concerned.

Because of all this, a campaign to reduce the number of deaths from appendicitis should be directed not toward individual surgeon's methods but rather, as has been mentioned, toward education of the laity as to the danger connected with procrastination and the use of laxatives.

Medicine presents its greatest service in the field of prevention. There is no honor in seeing through convalescence a patient with typhoid fever that could have been prevented. Similarly, there is no honor in removing a ruptured or gangrenous appendix which should have been removed before it ruptured. Unfortunately, the surgeon does not have for the prevention of appendicitis anything comparable to the preventive measures available for smallpox, diphtheria or typhoid. Because of the nature of the process it is difficult to conceive of any prophylactic measure other than removal of the appendix. I do not recommend that one should go to his physician for a prophylactic appendectomy as he would go to be vaccinated, although it is entirely conceivable that at some time in the future the prophylactic removal of the appendix will

involve no greater risk or reaction than do present day vaccinations. At present the anesthetic dangers, the risks connected with any surgical procedure and the possible bad results from the surgical procedure itself do not justify wholesale routine appendectomies. It is believed that a prophylactic appendectomy is justified and decidedly to be encouraged for any person who has had symptoms of appendicitis, no matter how mild, for recurrence of appendicitis is the rule rather than the exception. No one knows when this recurrence may occur or how severe it may be, and occurrence of an attack when one is on a hunting trip or otherwise isolated from the advantages of modern surgical skill might prove fatal. This has occurred sufficiently often in the experience of every surgeon practically to justify this type of prophylaxis.

The appendix will always be with man, for it is known that a race of persons who have all had their appendixes removed will not beget a race without an appendix. The appendix, like all degenerates, seems to be ever a bad actor, and never will the surgeon dare trust its behavior.

In reviewing the problem over a period of thirty-four years I sometimes wonder whether, instead of carefully preserving and sectioning each appendix and studying it pathologically, it might have been just as well to have saved the appendix and every so often to have gone on a fishing trip and used it for bait. If the appendix turned out to be wonderful fishing bait, probably many more persons would not procrastinate and take laxatives but would see the surgeon early so that they might use it for fishing. Appendixes then might be at a premium, and a markedly lowered death rate from appendicitis would no doubt be the result, together with a healthier race, benefited by the relaxation of fishing.

# OSSIFYING HEMATOMA AND ALLIED CONDITIONS

ARTHUR M. SHIPLEY, MD  
BALTIMORE

*Myositis ossificans traumatica* is the most frequently used term under which several more or less similar lesions are described. This name is widely used in the literature to designate a condition, not including ordinary callus, associated with the reaction of certain tissues to trauma. The structures involved may include the bone itself, the periosteum, the muscle and its fascial sheaths or the tendinous attachment of muscle to bone. Other names are used to indicate these abnormal bony masses: exostosis, *myositis ossificans circumscripta* and aberrant exostosis. Another condition bears a strong relation to this group and is sometimes included with it, the occasional formation in scar of bony tissue, especially after operation on the urinary bladder and in the upper part of the abdominal wall.

Ossifying hematoma is usually included in this group also, but this term is not widely used. In this condition the periosteum is believed to be stripped up from bone, and the space between the two tissues fills with blood, which is gradually replaced by osseous material. Whether this conception is accurate or not, the actual lesion is sometimes confusing, as it may bear enough resemblance to periosteal sarcoma to give the clinician, the roentgenologist and the pathologist a great deal of anxiety.

These conditions should be sharply differentiated from the calcareous and bony deposits associated with chronic infection, from all tumors of bone and from the various bony dystrophies.

The occurrence of aberrant bony growths in voluntary muscle, whether or not in contact with the underlying bone, has been recognized and recorded in the literature since the seventeenth century. In 1860 Bullrak differentiated two types of the condition. The first was the rather rare and fatally progressive form, usually commencing in the spinal muscles. The second he described as a localized, self-limited form involving a single muscle. By the end of the century sufficient cases had been added to the literature to make it apparent that the self-limited form was more than a curiosity and that it was associated with trauma in a high percentage of cases. Since then the rapidly increasing use

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Dr Roland E. Bieren aided in the collection of data for this paper.  
From the Department of Surgery, University of Maryland, and the surgical service of University Hospital.

of the roentgen ray has facilitated diagnosis, and many cases have been added to the literature. The incidence is undoubtedly higher than has been reported, as many patients are practically asymptomatic and either are not brought to medical attention or are discovered incidentally after the lapse of many years.

The name *myositis ossificans* is a confusing one. The lesion involves primarily the fascial connective tissue, any muscular changes being secondary and degenerative. Although there is frequent observance of histologic changes due to inflammation, this is the normal reaction of the tissues to hemorrhage. Actual infection is rare in connection with this lesion, except possibly as a secondary postoperative consequence. After the osseous mass is removed it is usually impossible for the pathologist to determine whether the bony tissue was attached to bone, developed in muscle or other tissues of the body or was removed from an operative wound or a sinus tract unless portions of the surrounding structures are attached to the specimen.

There are three anatomic possibilities as regards the bone itself and the attached or adjacent muscle.

1. With the first type there is involvement of the bone without extension into the muscles. Excluding from consideration true bone tumors, the cartilaginous and bony overgrowths associated with growth and hormonal disorders and the osteodystrophies, there are found a number of lesions that cannot be differentiated from *myositis ossificans* histologically. The process is the same, *i. e.*, abnormal osteogenesis. The only difference is that there is no extension into adjacent muscles. The simplest example of this type is the overenlargement of normal bony prominences often seen in the bones of the extremity in muscular, well developed persons. This falls within the limits of reasonable hypertrophy. When, however, this condition progresses to the point of functional disability or the formation of a definite mass it must be considered pathologic. "Rider's bone" is an example of this type, and the bayonet-like projections of bone into the soft tissues that have been reported from time to time belong in this classification also.

2. The second and most frequently described type of localized ossifying myositis is a combined lesion, in that it involves both the muscle and the underlying or adjacent bone. The bony mass may be firmly or only partially attached to the shaft and may extend for varying degrees into the muscle.

3. The third type is that occurring entirely in the muscle with no demonstrable connection to bone and usually with a well defined capsule or periosteum-like covering of its own. There might also be included in this group certain of the aberrant sesamoid bones. Perhaps lesions

which are frequently described as solitary localized exostoses may be the result of processes similar to those involved in myositis ossificans

Aberrant osteogenesis is not limited to the skeletal system and voluntary muscles. True bone formation has been described as occurring in the meninges, brain, arteries, lungs, lymph nodes, stomach, kidney, renal pelvis, ureter, bladder and skin, as well as in benign and malignant tumors and, indeed, almost anywhere in the body.

The mechanism of aberrant osteogenesis has been satisfactorily explained in two ways. The first is by overstimulation of normal osteogenic processes and necessitates the presence of normal bone or of detached fragments of periosteum or bone. This has been amply demonstrated by clinical and experimental evidence. The second mechanism is that of metaplasia of connective tissue cells into bone-forming tissue. The occurrence of metaplasia has long been recognized by pathologists and experimental workers, although its exact mechanism is obscure.

The following etiologic observations seem reasonable and well established.

1. Aberrant osseous formation is not a normal reparative process. If it were it should follow many fractures and contusions, whereas its occurrence following fracture is rare, and it does not often result from closed injuries of fascia or other tissues.

2. The most frequent single etiologic factor is trauma of the closed type, either single and severe or repeated and chronic.

3. Hereditary predisposition has been suggested. There is not yet sufficient information to give this belief any support.

4. The systemic condition of the patient has not been observed to be significant. The lesion commonly occurs in healthy, well developed persons. The values for blood calcium, phosphorus and phosphatase, when reported, have shown no deviation from the normal. There has not been demonstrated any disturbance of the acid-base balance of the blood. There has been no evidence of parathyroid or any other hormonal imbalance.

5. Most observers believe that the local reaction of the tissues involved is the important etiologic factor in all of these lesions. Just what conditions are necessary to the formation of these lesions is not understood. Extravasated blood may play a part. Certainly calcium, phosphorus and phosphatase are apt to be present.

6. It has been suggested that the presence of synovial membranes has favored the development of these lesions in some instances, especially about joints. There has been little evidence to support this view. The converse is more apt to be true.

There is no definite age incidence. Myositis ossificans, as usually described, is more apt to be seen in young, active persons, because these

are more liable to injury. The same is true of ossifying hematomas. The bony outgrowths believed to be due to excessive activity of certain muscles or tendons at their skeletal attachments should develop during the active years of life but may not be evident until later.

Certain muscles are predisposed to the development of myositis ossificans. The neighborhood of the elbow joint is a favorite site, either in the brachialis anticus muscle or lateral to or behind the joint as a late complication of backward displacement of the elbow. Two other muscle groups are predisposed, by reason, perhaps, of exposure to trauma, the quadriceps extensor and the adductors of the thigh.

The development of the chronic type of lesion is usually complete when seen. This fact is a valuable aid in differentiating these osseous masses from sarcoma. Trauma may be definite, or it may be obscure or even absent. The history is that of gradual development or the sudden noticing of a firm mass which usually is not tender or is only slightly so. If it is in a position where it causes pressure on important structures, the annoyance suffered by the patient calls it to his attention. If it is in a silent location it may be present for years before it is incidentally discovered.

The course of the acute lesion is more clearcut. After trauma a mass develops. This is clinically diagnosed as hematoma. It is somewhat doughy, and in the subsequent six days to three weeks, instead of resolving it becomes firmer and may even increase in size. This is, in turn, followed by definite ossification demonstrable by roentgen examination. Bone spicules have been seen roentgenologically as early as six days after injury, and distinct ossification is usually present at the end of six weeks. When there is no involvement of nerves or joints there are few subjective symptoms. The presence of a mass and slight tenderness to firm pressure are often the only evidences of trouble.

Growth is self limited and usually tends to become stationary after six weeks, but the mass may vary in size and consistency over a period of six months. There are some reports of gradual disappearance of the lesion without treatment. In many cases there are both clinical and roentgen diminution before the mass becomes stationary.

When an area of myositis ossificans is exposed at operation it is usually found surrounded by a semigelatinous substance which appears to be the result of muscle degeneration. Just under this tissue there is usually found a fibrous capsule that acts much as periosteum does in separating bone from surrounding structures. If the mass is subperiosteal it has no capsule of its own and is entirely beneath the displaced periosteum of the bone involved, as in exostoses or osteoma. If the mass extends into the adjacent muscle its capsule may be continuous with and is probably partly at least derived from the periosteum of the

underlying bone. Usually the periosteum and the capsule are indistinguishably fused at the junction. Cystic changes are not infrequently observed.

Histologic examination in the early stages shows organization of blood clot, hyperplasia of connective tissue and degeneration of muscle fibers (when muscle is involved). Some degree of chronic inflammation typical of tissue reaction to interstitial hemorrhage is usually observed. This is followed by the appearance of islands and spicules of osteoid tissue. Islands of cartilage are of frequent occurrence and are apt to be seen in the earlier stages. The late appearance is that of adult organized bone with marrow cavities, an organized fibrous stroma and a definite tendency of the peripheral portion of the mass to form a capsule. Simple calcification of connective tissue may also be present. Myxomatous tissue is not uncommon.

It is interesting to note that lesions removed during the course of spontaneous resolution may show definite osteoclast activity, with bone destruction and absorption. It is also interesting to note that occasionally a few of these lesions behave like normal bone in being subject to attack by further pathogenic processes. In 1 case observed by my associates and me, previously described by Cone, there was a resemblance to *ostetis fibrosa cystica*, with gross cysts and numerous giant cells. In a case collected from the literature and in 1 of our own cases there developed a spontaneous, apparently hematogenous suppurative process analogous to acute osteomyelitis. Four cases have been recorded in the literature of the development of osteogenic sarcoma in preexisting myositis ossificans traumatica. No records have been obtained of the subsequent involvement of these lesions by tuberculosis or syphilis, although the possibility of such involvement seems not unlikely.

In a paper read before the Western Surgical Association in December 1922, Dean Lewis reported his experience with myositis ossificans and discussed the interesting bony masses that are occasionally found in the scars of abdominal incisions. These masses are most often seen after operations on the stomach or urinary bladder. The acid gastric juices and the urine raise an interesting question. Bony infiltration of these scars is usually explained by metaplasia, but it is difficult entirely to exclude detached bits of periosteum in suprapubic cystotomies, and Lewis has called attention to the fact that a *linea transversa* in the rectus muscle represents the remains of a rib that at one time extended toward the midline of the abdomen. The undifferentiated mesoblastic cell of the embryo may remain quiescent into late adult life, and these cells of the mesenchyme may well explain many of the extraskeletal bone masses reported in the literature on this subject.

Phemister and Strauss showed that fascial transplants placed in the stomach, urinary bladder and ureters became infiltrated with bone. It



is known that normal osteogenesis necessitates a relatively high concentration of ionizable calcium and phosphorus in the blood serum and that phosphatase is involved in some way in the process. In addition, there must be a relative alkalinity of the acid-base balance of the ossifying tissue for the calcium to be deposited as calcium carbonate and tricalcium phosphate. It seems not unlikely that a local setup of the mechanism in the tissues following injury or insult might result in ossification.

Ossifying hematoma or subperiosteal blood clot with osteogenesis has been reported by a number of observers. Baetjer and Waters, in "Injuries and Diseases of the Bones and Joints," described the condition. Stone reported 6 cases in 1926, and his findings were definite.

In each of the foregoing there was a hard blow and then a hematoma which decreased in size and later ossified. They were all under the periosteum. This would make it appear that following the injury there was bleeding next to the bone. The periosteum was pushed up and gradually stretched into various shapes, in which position ossification took place. Each tumor was bone entirely covered by periosteum. Muscle was attached to the outside, but not once was it found inside the mass. This should be proof that it is not an ossifying myositis.

Bullitt reported a case in 1927, Chiari reported a case in 1917, and Riddle and Wilson, of Plymouth, England, described such a lesion in 1926.

In a considerable series of cases of the allied conditions just described there have been 2 that caused my associates and me a great deal of uncertainty as to diagnosis and anxiety as to proper treatment. Both are now believed to have been cases of ossifying hematoma developing in close relation with stripped-up periosteum following trauma, and in both the question of diagnosis was the important factor, because both patients were sent to us with a diagnosis of sarcoma already tentatively made.

#### REPORT OF CASES

CASE 1—An 18 year old girl, while riding, was thrust against a projecting staple in a post by the shying of her horse. A somewhat tender area developed in the region of the left deltoid muscle. The pain subsided, but the mass continued to grow. At the end of about three months roentgen examination was made in her home city, and the condition was diagnosed as osteogenic sarcoma of the upper end of the humerus. Amputation of the arm was advised. She was brought to us for consultation by her parents, together with the roentgenograms. The mass was the size of an orange and clinically looked like osteosarcoma. The history of trauma, however, made us hopeful that the lesion might be an ossifying hematoma, but there was a history of steady growth and considerable pain. The roentgenograms were not conclusive, however, although the bony mass was mottled, and there was a faint cortical shadow indicating some walling off of the tumor from the soft parts. There was no evidence of metastasis to the chest. Dr. Henry J. Walton, the roentgenologist, leaned toward the diagnosis of a benign outgrowth, rather than osteosarcoma. The patient therefore returned to her home, and her

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# SURGICAL PROBLEMS IN THE TREATMENT OF CHRONIC ULCERATIVE COLITIS

HARVEY B. STONE, M.D.  
BALTIMORE

Those who have had the unwelcome duty of caring for any considerable number of patients with chronic ulcerative colitis of the so-called idiopathic form realize that the condition presents many problems. In spite of much conscientious work and many ingenious theories, its cause still eludes discovery. The medical care of these patients is by no means acceptably standardized. Relation to other disorders and to complications is obscure. The prognosis is very uncertain. The clinical course is full of surprises and disappointments. Recurrence after years of apparent cure is well known, and sudden exacerbation of long-standing, mild forms may take place.

It is not with such phases, however, or with the handling of the surgical complications, such as perirectal abscess, fistula or stricture, that this paper is concerned, but rather with the proper place of surgical measures in the treatment of the disease itself. There is wide difference of opinion as to this place. It would seem that there is a large group of physicians who either are unaware of or disbelieve in the utilization of operative treatment for ulcerative colitis. On the other hand, many of the leading medical authorities on the condition fully accept the need for surgical intervention at certain times and in certain conditions but have no unanimity as to what these times and conditions are. The same situation exists among surgeons. In various publications from the Mayo Clinic the impression is given that surgical intervention is a bad last resort. By other clinics and other surgeons the earlier employment of operative treatment is advocated. The present paper aims to discuss this problem and perhaps to introduce clearer criteria for decisions about the part to be played by surgical measures in the treatment of ulcerative colitis.

One must first understand what surgical attack can hope to do. After a period in which appendectomy and cecostomy were employed to permit irrigation of the diseased colon from above downward, the failure of this idea has been generally admitted by surgeons experienced in this field. These operations have been abandoned in favor of complete transverse ileostomy a short distance above the ileocecal valve. The principle employed in this method has nothing to do with irrigation of

the colon from above but is designed to put the large bowel completely out of function and give it physiologic rest. This is the principle employed in the treatment of tuberculous disease of the spine and of the hip by the use of immobilization. It is the principle of collapse of the lung for pulmonary disease. It goes back to the epochal work of Hilton on "Rest and Pain." The inflamed and damaged colon no longer has to transport the ingested food. Its peristalsis is greatly reduced, and distention and mechanical irritation are lessened. These changes favor the healing and reparative forces. This is sound theory, and ample experience of many surgeons and physicians has shown that the theory often works.

The theory, however, does not always work. The clinical course of a patient after ileostomy may follow one of three directions. The colon may heal completely, permitting safe closure of the ileostomy opening and restoration of the large bowel to its normal function. Unfortunately, in few cases does the condition behave in this desirable manner. More will be said about this fact later, indeed, the purpose of this paper is to increase the number of cases falling in the group, in which this occurs. The second course taken after ileostomy may result in great improvement in the patient's general condition, but with persistent evidence of the disease in the large bowel. This is the situation that led the late Daniel F. Jones to say that ileostomy cures the patient but not the disease. There is often a surprising gain in weight, strength, blood cells and general well-being, but there persists a more or less frequent discharge of blood, pus and mucus from the rectum. The proctoscope shows persisting evidence of inflammation in the rectum and in the lower part of the sigmoid flexure. The barium sulfate enema shows a rigid colon with loss of haustration. It is obviously unsafe to reestablish the alimentary tract by closure of the stoma, as a rapid recurrence of active trouble is to be expected. The process is arrested but not cured. In the great majority of patients subjected to ileostomy this course is followed. It is an unsatisfactory situation. Their lives may have been saved, but at the price of a permanent ileostomy opening. A third outcome may follow ileostomy. The progress of the disease may not be arrested. Progressive fever, bleeding, loss of weight and anemia may occur. The pathologic changes in the colon may lead to a diffuse polypoid condition of the mucosa, and in some such cases malignant disease may develop. To save the patient the heroic measure of colectomy must often be invoked. This last course of events, like the first, occurs in a smaller number of cases than does the second (arrest of the process without cure).

The obvious problem for the surgeon is to find a way of greatly increasing the first, or completely successful, type of result. To approach a solution, one may ask the question. Why do some lesions heal com-

pletely after ileostomy? In the present state of ignorance as to the real cause and nature of the disease it would certainly be presumptuous to venture a complete answer, but it is at least reasonable to suppose that one factor in the situation is the employment of the principle of rest for the colon before that organ has suffered irreversible pathologic changes. One such change is the extension of the inflammatory process from the mucosa into the other coats of the bowel wall, with deposition of scar tissue and conversion of the thin-walled, flexible, contractile intestine into a stiff, thickened and shortened pipe. There is at least some information obtainable as to when this change has taken place. The barium roentgen study of the colon will indicate beginning loss of haustration, stiffening and shortening. It is one of the cardinal purposes of this paper to urge that ileostomy be employed *before* such alterations are detectable, or at least that the earliest indications of them in roentgen studies be considered sufficient warrant for operation. There is surely reason to think that such a criterion would notably increase the percentage of cases in which the patient is "cured" by operation.

Why does one need to set up a guidepost for operation? If early operation offers so much possibility of improved results, why are not all patients operated on early in the disease? The answers are not difficult to find. In the first place, the unpredictable course of the disease causes reluctance to resort to radical measures prematurely. In a great many cases, even in some of those in which the onset is violent, the condition abates and apparently clears up under less radical forms of treatment. It is natural to hope in each instance that this may take place and to defer surgical attack from time to time in this hope. For this reason frequent study of the roentgen appearance of the colon may prove a useful and practical guide to the onset of changes that no longer brook delay. A second and potent reason for hesitation to resort to ileostomy is the nature of that treatment itself. When an artificial anus is made through the abdominal wall, there results the need to care for fecal discharges, the trouble of providing and wearing dressings or apparatus of some sort and the disagreeable odor or fear of odor, which is most distressing to sensitive patients. When the fecal fistula opens from the ileum there is, in addition, often much difficulty in keeping the abdominal skin about the stoma in good condition. In many such cases a widespread excoriation of the skin develops in spite of all efforts to prevent it, and this is extremely painful. At times a considerable prolapse of the ileum may occur, with protrusion of a long piece of intestine, that adds to the discomfort and difficulty of caring for the ileostomy. This may require a secondary operation to correct it. One need not elaborate further to prove that treatment by ileostomy carries with it many disadvantages, indeed, as some have expressed it, the treatment may be as bad as the disease. There can be no doubt that this aspect

of the matter has had great deterrent influence both with patients and physicians against the early employment of ileostomy. A third objection is the probability that, once made, the ileostomy opening may have to be retained permanently because of failure of the colon to heal. These, then, are the very powerful influences against early resort to ileostomy. Yet, in my experience, later successful closure is obtained only when early ileostomy has been employed. It would seem proper to urge the surgeon and the patient not to trust too much in a turn for the better, to look frequently for beginning evidence of roentgen changes and to adopt the plan of treatment by ileostomy at the first sign of such changes.

This doctrine would be more readily accepted if surgeons could devise some type of operation to reduce the distressing features of ileostomy. A step in this direction has been made by Cattell, of the Lahey Clinic, who draws out the stump of the ileum several centimeters beyond the level of the abdominal skin and fixes it there. This projecting ileal stump can be inserted into the rubber bag which is worn during the day and thus permits the collection of fecal discharges with less soiling and irritation of the skin. I have employed another device in 1 or 2 cases that may prove helpful also. A young man was seen a year or two ago, whose ileostomy opening, created elsewhere, gave great trouble because of intussusception of the bowel above the stoma through that opening. There frequently resulted protrusion of a segment of intestine 20 to 30 cm long, which soon became edematous, purplish and greatly swollen, with consequent difficulty in reducing the prolapse. Relief for this condition was sought, and in attempting it a method was devised that not only corrected the prolapse but in considerable measure altered the character of fecal drainage. There was more absorption of fluid, with a less liquid stool and less frequent evacuations.

In brief, the abdomen was reopened, and the ileum just above the stoma, which had not been disturbed, was drawn into a U-shaped loop immediately proximal to the stoma. Each arm of this loop was about 20 cm long. The two arms were sutured to each other, and then a wide lateral anastomosis was made, running the whole length of the adjacent arms (see accompanying sketches). The ileum was then replaced in the abdomen and the wound closed. Two results were sought by this procedure. First, the bulky, self-anastomosed loop just above the stoma effectively stopped the prolapse. Second, this loop with its anastomosis formed a reservoir and peristalsis-checking trap for intestinal contents, which it was hoped would slow down discharges and aid in absorption of fluid. The latter effect was attained in part at least, the patient reporting definite improvement in this respect. Barely a beginning has been made with this method, and certainly no conclusions are possible as to its value. Perhaps combined with Cattell's

projecting stump it would be more effective. The purpose in mentioning it here is to raise the problem of operative means of delaying peristalsis and promoting absorption in the ileum above the ileostomy and to stimulate surgeons in the solution of this problem.

There is another issue of great practical importance in the handling of patients after ileostomy—to determine when the stoma may be closed with reasonable safety. This cannot be based on the general improvement of the patient. It is not uncommon to see remarkable gains in weight, with restoration of the blood to normal and absence of fever or any abdominal symptoms but with persistent ulcers in the “defunctionated” colon. Proctoscopic examination, of course, gives direct evidence of the condition of that part of the bowel that can be inspected, and until this area has returned to normal appearance there can be no

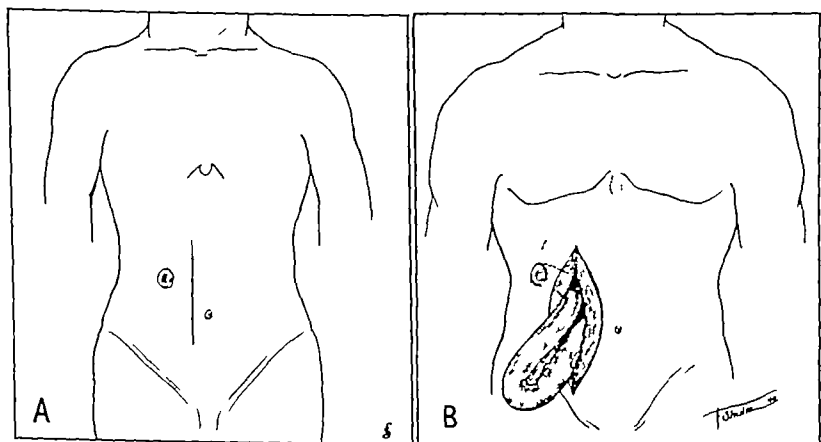


Fig 1—A, right rectus incision mesial to the ileostomy, B, loop of ileum just above the ileostomy, drawn out through the incision.

thought of closure of the stoma. For the higher portions of the colon, roentgen enema studies are helpful in indicating the return of flexibility and distensibility to the wall of the bowel. Another test, seemingly not widely known, has proved of much value. When the colon apparently is approaching normal, 1 liter of physiologic solution of sodium chloride is introduced into the rectum and, when expelled, is centrifuged. The sediment thrown down is examined microscopically. If a considerable number of red corpuscles and leukocytes are found, it is evident that an active inflammatory process persists in the bowel. When these finally disappear, one may safely assume that the time has come to close the stoma. In my rather limited experience this has proved a reliable guide to safety of closure.

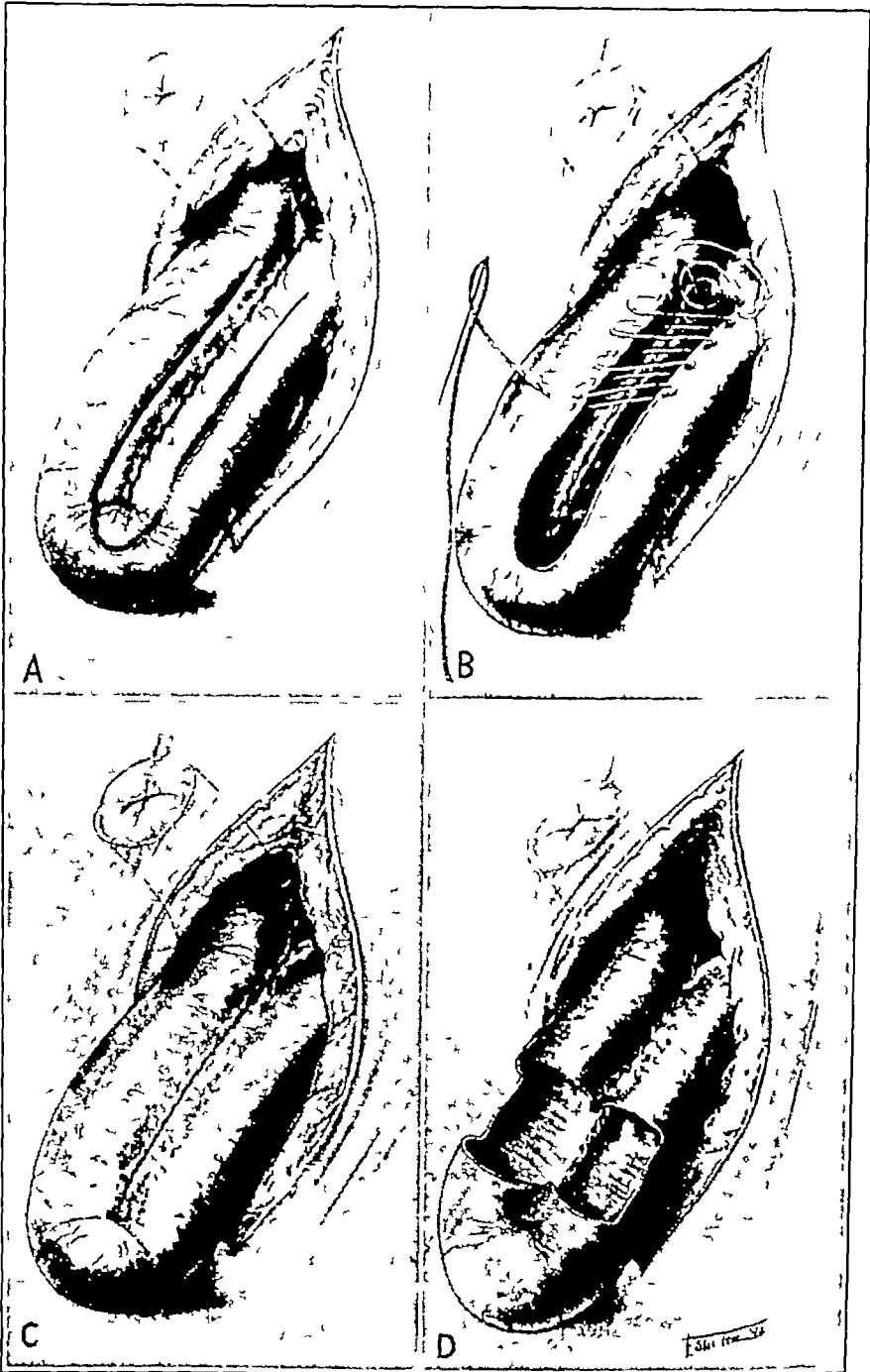


Fig 2—*A*, the two arms of the loop are sutured to each other with a continuous silk suture, and a U-shaped incision is begun in the adjacent arms of the loop *B*, anastomosis between the two arms of the loop The second row of sutures at the back, consisting of a continuous catgut stitch, has been completed, and this stitch is continued as a suture between the two anterior edges of the incision *C*, second row of anterior continuous silk suture The anastomosis is completed *D*, diagrammatic sketch with removal of a window in the anterior wall of the loop to show the side to side anastomosis



Another group of surgical problems is raised by those patients who fail to improve after ileostomy and whose lives perhaps can be saved only by total or subtotal colectomy. These problems concern the indications for colectomy, the preparation of the patient and the execution of the resection in stages. Since these questions have already been adequately considered by others and I have no particular addition to make to this phase of the general subject, comment will be limited to calling attention to their great practical importance in treatment of the most serious type of chronic ulcerative colitis.

#### SUMMARY AND CONCLUSIONS

Ileostomy before permanent damage to the colon takes place is the best chance of securing a return to normal conditions, and roentgen studies of the colon are a guide to the time when it should be employed.

Improvement in the type of operation should be sought to render ileostomy a more acceptable form of treatment.

Methods of determining when the stoma may be closed with safety are described.

## LUDWIG'S ANGINA

HUGH H TROUT, M D

ROANOKE, VA

Isadore Auguste Marie Francois Xavier Comte, a French philosopher who lived from 1789 to 1857, originated the dictum "You can know little of any idea until you know the history of that idea"

Perhaps all physicians have speculated to themselves as to what concept or idea has fixed the name of Wilhelm Friedrich von Ludwig (1790-1865) to a pathologic condition so firmly that the attachment has existed for over a century in spite of the natural opposition of the members of the medical profession to the association of proper names with symptoms, signs or diseases

In fact, this hostile attitude toward retention of von Ludwig's name in association with the morbid changes he described became so acute that in 1892 a heated debate on the subject took place between Délorme and Nélaton

Even in the United States, Ashhurst, as an invited guest of the Western Surgical Association in 1929, remarked when discussing Ludwig's angina before that society that there were two schools of thought as regards the classification of diseases. One group followed the teaching of Hippocrates in objecting to the unnecessary multiplication of names of diseases and preferred to assign the so-called new diseases to their proper place under already recognized pathologic processes. The other school of thought—the Cridians (of whom I never heard until I read Ashhurst's address)—considered every new symptom and every new complication to constitute a new disease.

It is not necessary for one who knew Dr Astley Paston Cooper Ashhurst to state that he advocated the principles of Hippocrates in this respect and did so with all the vigor and convictions of a most capable surgical philosopher.

It is interesting to recall that Ludwig's angle, the angle situated between the manubrium and the gladiolus, derived its name from Daniel Ludwig (1625-1680), a German anatomist. Furthermore, Ludwig's ganglion, a ganglion connected with the cardiac plexus and situated near the right auricle of the heart, obtained its name from still a different Ludwig, namely, Karl Friedrich Wilhelm Ludwig, a German physiologist (1816-1895). However, Karl Friedrich Wilhelm Ludwig's name is not attached to any of the many recording instruments which he introduced into physiology.

In the year 1836 a great tragedy befell the German kingdom of Wurttemberg. The beloved Queen Catherine died, and her death was due to a condition concerning which the physicians of that time had little knowledge. The affliction which caused her death was described as a "sublingual phlegmon." It is interesting to recall that when Queen Catherine died there was no dental school in Germany. In fact, her death occurred four years before the founding by Dr. Chapin A. Harris and Dr. Horace H. Hayden of the Baltimore College of Dental Surgery in 1840, which is accredited with being the first school of dentistry in the world.

I am unable to ascertain whether Queen Catherine's illness followed the extraction of a lower molar tooth, but if it did, I feel confident that she displayed Spartan courage, as strength and brute force were the only dental requirements in vogue in that period.

Shortly after the death of this popular queen, Prof. Wilhelm Friedrich von Ludwig, vice director and *Leibarzt* of the Stuttgart Hospital, at the age of 20 years addressed a medical meeting then in session in that city. He selected as the subject of his address the condition from which the beloved monarch had so recently died. About a year after this address, Camerer designated the pathologic process from which Queen Catherine died as Ludwig's angina, and as such it has been known for over one century.

Perhaps it would be both interesting and instructive to review the criteria expounded over a century ago by von Ludwig and by such a study to estimate how much the tragedy of Queen Catherine's death had to do with the continued association of von Ludwig's name with the pathologic process which caused the death of such a popular ruler.

Von Ludwig considered that the following conditions should be present in order to establish the diagnosis of the condition to which his name had been attached for so many years:

- 1 There should be inflammation of the deep cellular tissues under the tongue.
- 2 The inflammation should begin around the submaxillary salivary gland.
- 3 The inflammation should subsequently invade the neck and the floor of the mouth.
- 4 The condition should run a course which grows progressively worse, with death in ten to twelve days or gradual recovery.

Dr. John Burke, of the Buffalo City Hospital, presented an excellent translation of "Angina ludovici," together with a biography.<sup>1</sup>

I think most physicians will agree that these requirements are sufficiently indefinite to explain the great discrepancy of the mortality statistics published in reports of deaths from Ludwig's angina.

<sup>1</sup> Burke, J. Angina ludovici. Translation, Together with a Biography of Wilhelm Friedrich von Ludwig, *Bull. Hist. Med.* 7 1115-1126 (Nov) 1939.

Certainly a study of the various operative procedures and methods of treatment does not disclose a sufficient difference in surgical methods to explain the great variation in the relative number of deaths reported by the various authors, the highest mortality percentage being 75 and the lowest only 5

This being the situation, it is reasonable to assume that there exists today a marked difference of opinion as to what actually constitutes Ludwig's angina



Fig 1—Wilhelm Friedrich von Ludwig Presented by Dr Fordyce B St John, of New York

However, I believe that most surgeons of the present time agree with those essayists whose mortality statistics vary from 30 to 75 per cent These surgeons include among cases of Ludwig's angina only those in which the patient is desperately ill, sometimes fighting so hard for breath that an emergency tracheotomy is indicated even before any attempt is made to release the tension in the neck

While the condition is usually a rapid process, it is also progressive, with different symptoms and signs at different stages of its progression

Therefore, the treatment of this disease is necessarily like that of many other surgical conditions in that a careful, separate study of each individual patient is required

A recent review of reported cases revealed that when the etiologic factor was indicated the condition followed extraction of the lower molars or the posterior bicuspid in 82 per cent of such cases. In the remaining cases such etiologic factors as calculus in the submaxillary duct, infection of the sublingual and submaxillary glands, injury to the floor of the mouth by pieces of foreign bodies being held in the mouth and infected fractures of the lower mandible were found.

Numerous studies of the various bacteria found in the cellular tissue under the tongue after incision discloses many different types of organisms, and to a large extent bacteria of the same type are also found in tooth pockets both before and after the extraction of teeth. In this group of organisms are to be found many different types of streptococci, spirochetes and the fusiform bacilli of Vincent and Plaut.

To mention streptococci at present almost automatically brings to mind the possibility of the employment of sulfanilamide or one of its derivatives both in prophylaxis and in treatment of this type of infection.

The extraction of a lower molar tooth is not, as a rule, a major dental problem, but any operative procedure done in an infected field means that there is a chance of extension of the infection unless the general system of the patient creates a sufficient defense to limit the invasion. Sulfanilamide can be given by mouth, under the skin, by rectum or intravenously in quantities to produce a concentration of the drug in the blood stream sufficient to prevent the growth of the streptococcus and often to kill this organism even after the infection has extended beyond the jaw.

If the gums or teeth to be extracted are badly involved in an infection, it may be a wise precaution to develop in the patient a concentration of sulfanilamide in the blood adequate to prevent further spread of the infection. This should be done only with the cooperation of a well equipped clinical laboratory. Sulfanilamide is not without its dangers when administered without the tests, both clinical and laboratory, so necessary for safety. To produce the desired results in such a patient would require several days at the least. However, as a rule the condition of the patient who is to have a lower molar tooth extracted is such that delay of this extent would not be dangerous and might add considerable safety to the extraction of the tooth. It is considered by those familiar with sulfanilamide that the drug has a distinct place in the field of prophylaxis in the extraction of teeth in infected fields.

The natural question that now arises is *What is the field of application of the drug when the infection has clinically extended beyond the primary infected field?* The drug might be of definite aid under such conditions, but such treatment carries with it one very dangerous

possibility, namely, postponement of operative relief of tension and of extension of the infection while one is watching for the favorable effects of the drug. Certainly under these circumstances sufficient time cannot be taken even to test for or to attempt to establish proper levels of sulfanilamide in the blood.

I feel sure, from my experience in other fields of infection, that the administration of sulfanilamide or of one of its derivatives after the

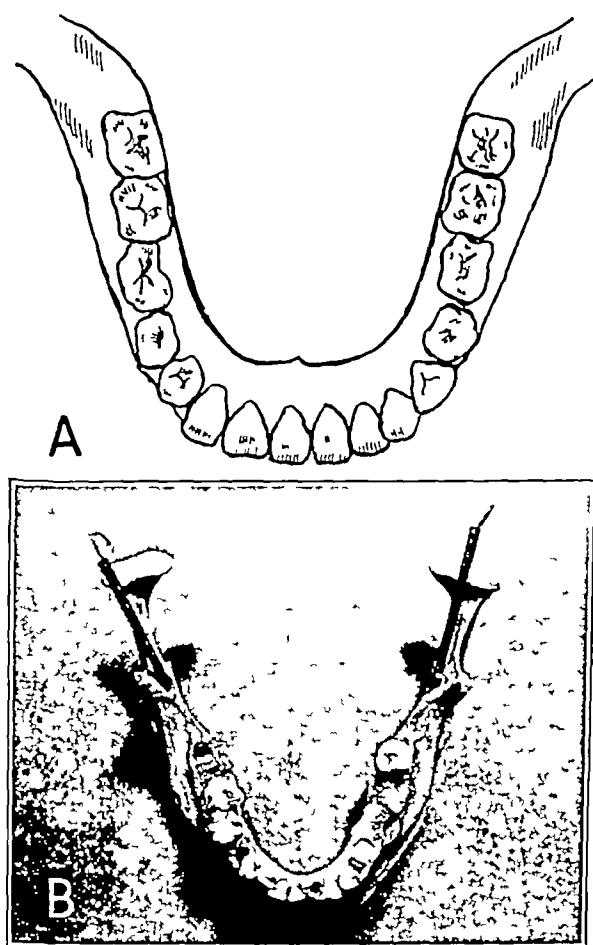


Fig 2—*A*, diagram showing the molar tooth "off center" and toward the mid-line and the anterior teeth "off center" and toward the outer side. *B*, photograph of the lower mandible, showing the same relation diagrammatically presented in *A*.

relief of tension and the establishment of proper drainage of the infected field will prove to be of considerable aid in postoperative recovery provided the drug is administered with proper care and control. It has been demonstrated that from 12 to 15 mg of sulfanilamide to 100 cc of blood is necessary for the maximum benefit. Such a concentration cannot be obtained quickly if the patient is allowed to consume his usual quantity of fluid, therefore, in order to bring up the blood concentration of sulfanilamide rapidly to the desired level, the fluid intake of the patient is limited to 3000 cc or less for twenty-four hours.

Sulfanilamide employed as a fine powder has been found of advantage when placed in the tooth pocket after extractions

Sometimes there is an ulcer found over an unerupted molar tooth and under the gum when the mucous membrane is incised in order to extract the tooth. Frequently anaerobic bacteria are associated with such ulcers. In such instances zinc peroxide as advocated by Meleney has been found valuable.

The employment of roentgen rays as an aid in the treatment of infections in the sublingual and submaxillary spaces carries with it the usual dangers associated with delay in the handling of any treacherous and rapidly progressing disease which requires immediate surgical relief of tension to prevent fatal strangulation.

In addition to the usual dangers, there is the added probability that after irradiation there will be an increase of tension due to the physiologic reaction stimulated by the roentgen rays.

As one reviews, even by a brief method, a study of the anatomy of the lower jaw and neck there stand out two very important anatomic considerations in relation to infections in this region. The first of these considerations is the fact that the tooth sockets are not in the midline of the lower mandible but are "off center." The molar sockets are closer to the inner than to the outer side. This, of course, means that there is a very much thinner partition of bone separating the socket cavity of the molar teeth on the inner side than on the outer side.

In addition to this anatomic fact, it is important to recall that the molar teeth are separated from the underlying fossa of the lower mandible only by a relatively thin partition of bone (fig 3).

In the existence of these anatomic differences is to be found the explanation of the fact that infections are more frequent on the inner than on the outer side. Naturally, the reverse of this situation exists regarding the front teeth.

Of course, the clinical application of these anatomic observations is to be found in the fact that one can reasonably expect that any infection following extraction of the front teeth will either soon show superficial fluctuation or gradually subside. Infections following such extractions can be watched without endangering the patient's life, but this is not the case with infection following extraction of the molars, for infections of this type tend to be deep and hidden under the tongue.

The other anatomic consideration of great importance is the fact that the mylohyoid muscle is hung like a broad hammock from the lower mandible to the hyoid bone. Superficial to this muscle and reinforcing it is to be found the deep cervical fascia of the neck. These two structures (the mylohyoid muscle and the deep cervical fascia) therefore tend to confine infections following extractions of lower molars to the deep tissues under the tongue (fig 4).

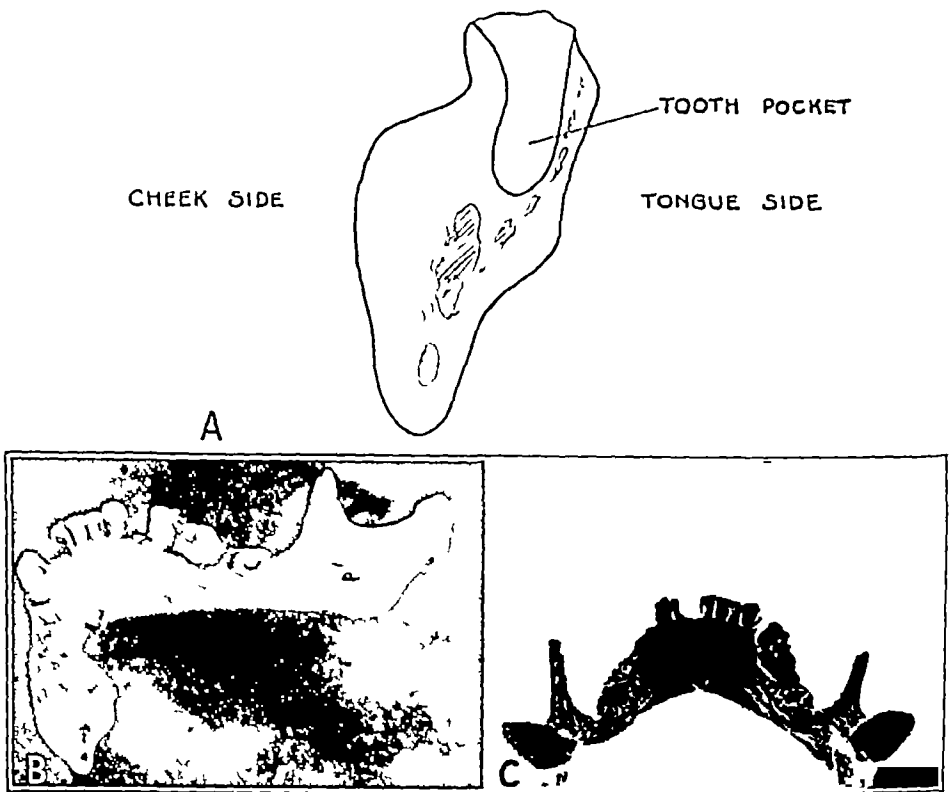


Fig 3—*A*, diagram of transverse section through the second molar indicating how much closer the lower part of the tooth pocket is to the tongue than to the cheek *B*, section of the lower mandible through the second molar tooth, showing the relation diagrammatically presented in *A* *C*, photograph emphasizing how the posterior portion of the lower mandible hangs like a shelf over the floor of the mouth

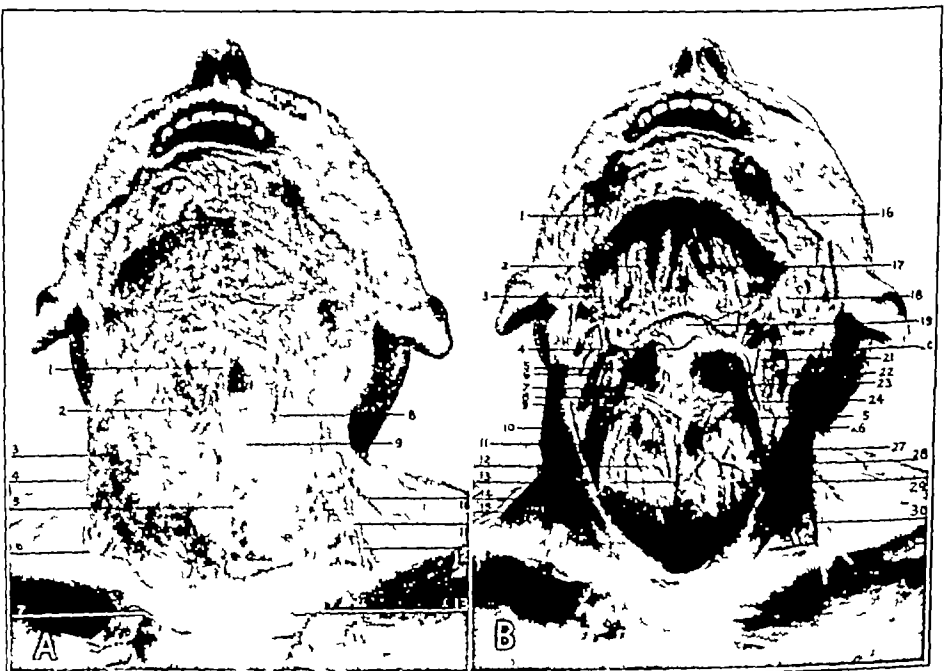


Fig 4—*A*, the superficial fascia *B*, the mylohyoid muscle The drawing demonstrates the attachment of this muscle to the hyoid bone. It also indicates the necessity of cutting the muscles transversely in order to release pressure on the hyoid bone. (From McClellan, G Regional Anatomy in Its Relation to Medicine and Surgery, Philadelphia, J B Lippincott Co, 1892, vol 2, plates 23 and 24 )



Infections confined to the sublingual and submaxillary spaces under the tongue are the type usually included under the term of Ludwig's angina. It is this type of infection which in my opinion requires the combined vigilant attention of both the dentist and the physician. To be more definite, it is my deliberate opinion that if after extraction of a lower molar tooth a hard swelling occurs under the tongue it is the duty of the dentist to call into consultation the surgeon who may have to open up the neck widely and hurriedly in order to save the patient's life. I know of no more difficult decision than the selection of the proper time to operate for these infections. As a rule, there is no fluctuation to be felt in the mouth—in fact, very little pus is found at the time of operation. In the place of pus there is usually a large quantity of gangrenous material and other debris, such as is often found in other parts of the body where the tissues have been strangulated and the blood supply impaired.

As this swelling increases, the base of the tongue is pushed upward and backward toward the posterior part of the pharynx to such a degree as to interfere greatly with the patient's ability to obtain sufficient air through the trachea to supply the respiratory demands. Not only is the tongue pushed upward and backward, but increased tension is made on the mylohyoid muscle. With this increase of tension on this muscle, there is necessarily an upward and forward displacement of the hyoid bone. In several days and sometimes in a few hours this tension is so great as not only to pull the jaw down but to pull the hyoid bone forward and slightly upward. Of course, the fibrous attachments between the hyoid bone and the larynx are such that when the hyoid bone is displaced the larynx is carried with it. With the base of the tongue pushed backward to the retropharynx and the larynx pulled upward and forward, it is easily understood why the patient fights so frantically for breath (fig 5).

With a patient in this condition any anesthetic is dangerous. Frequently the patient's condition is such as to demand an immediate tracheotomy. This is usually done with the aid of local anesthesia, and then one of the gas anesthetic agents can be administered through the tracheotomy tube. If the patient's condition is not so desperate as to demand an immediate tracheotomy, one of the intravenous anesthetics, preferably sodium pentothal (sodium-1-methylbutyl-thiobarbituric acid) can be employed, but even then the tracheotomy set should be handy, as these patients sometimes have embarrassment of respiration after administration of any intravenous anesthetic.

Whenever an intravenous anesthetic is employed, it should be given by the intermittent fractional method of injection. Dr R. Charles

Adams has stated that pentothal sodium should not be given to a patient who has been receiving sulfanilamide, but Dr Perrin Long has expressed disagreement with this view. I know of no case in which there have been any disastrous consequences which could be attributed to such a practice. If the patient's condition is such as to warrant the employment of a general anesthetic, my preference is for ethylene. Preliminary administration of morphia and atropine sulfates aids in the giving of any anesthetic. Oxygen, carbon dioxide and coramine (a 25 per cent solution of pyridine betacarbonate in diethylamine) should be handy. The employment of helium in association with either nitrogen monoxide or ethylene has not yet reached the stage of practical application. However, helium can carry oxygen through greatly restricted

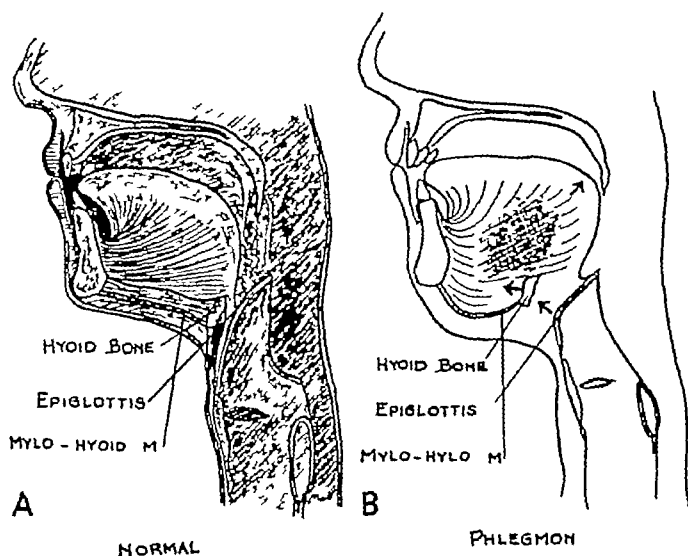


Fig 5—Diagrammatic sketches. Note that as the phlegmon increases it pushes up the tongue to the back of the mouth and pulls the hyoid bone and the epiglottis forward.

respiratory passages, and these patients frequently need quickly all the oxygen possible to be obtained.

Certainly if tension is to be relieved in these cases more than simple incision and drainage will have to be done, for as a rule very little pus will be found. Necrotic and gangrenous material should be removed. Rehn has advocated the routine removal of the submaxillary gland, but this gland should not be removed unless it is involved in the inflammatory process or is interfering with drainage. Care should be exercised to prevent the dissection from extending through the mucous membrane into the mouth.

Most authorities consider that in this type of infection, extension takes place through fascial planes and not by lymphatic channels. It is

also probable that extension can and does take place by both fascial planes and lymphatic routes. In any event, it is certain that free and full drainage is indicated.

In order to meet these indications the incision should start near the angle of the jaw and about  $\frac{1}{2}$  inch (1.3 cm) from the border and continue to the chin. If the infection is bilateral, as it frequently is, this incision should continue in the same manner on the opposite side of the jaw. It should continue through the deep cervical fascia to the muscles of the mylohyoid muscle. When the fibers of this muscle are reached they should be cut transversely. The anterior belly of the digastric muscle should also be cut transversely. By cutting these muscles in this manner the pull on the hyoid bone is released, which is not the case with any incision which enters the deep structures by simply separating the fibers of the mylohyoid muscle. I recall 1 case

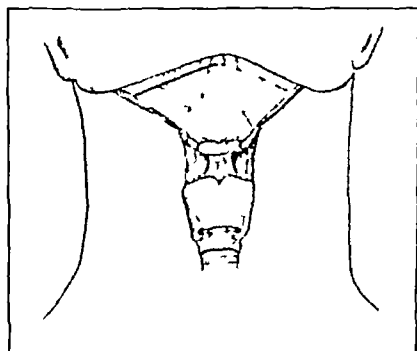


Fig. 6—Diagram to indicate the necessity for cutting the fibers of the mylohyoid muscle and the digastric muscle transversely if traction on the hyoid bone is to be released.

in which a transverse division of these muscle fibers allowed the larynx to drop back to its normal place, with great relief to the respiratory efforts of the patient (fig. 6).

The respiratory relief in this case occurred almost immediately and before the incision extended to the involved tissues under the tongue.

In a life-saving procedure such as this operation often is, no consideration should be given to the possible appearance of the scar after the patient's recovery, for only the saving of life is the objective of the surgical attack in such cases.

The incision is packed with gauze and left wide open so as to allow free and full drainage.

If considered advisable a simple, safe plastic operation in the future will often greatly improve the appearance of the scar, but this is seldom indicated.

# CARDIAL\* GASTRIC ULCERS

RESULTS OF OPERATION FOR APPARENTLY INACCESSIBLE LESIONS

WALTMAN WALTERS, M.D., Sc.D.

ROCHESTER, MINN.

Experience has shown that in the evolution of treatment cycles occur. This may be due to the changing incidence of the disease or to its severity. Of great influence, of course, are the results which follow different methods of treatment. Generally speaking, response to conservative methods of treatment is more likely to occur when economic and social changes have improved the general health of the community. Under such circumstances, routine methods of therapy may produce an increasing incidence of benefit or cure, which increases further when unproved methods of therapy are developed and instituted.

These remarks apply particularly well to the treatment of gastric ulcers. As a result of a better understanding of these lesions and their earlier recognition, while the lesion is still small and without the complicating features of hemorrhage, perforation and obstruction, relief of symptoms and healing of the ulcer have resulted from a medical regimen in more cases recently than many years ago. The only objection to a medical regimen in all such cases is that in some of them the lesion, instead of being a small gastric ulcer, is in reality ulcerating carcinoma. In many such cases roentgen or gastroscopic examinations will not assist in the differential diagnosis (table 1). It has been said that a trial course of medical treatment serves as a diagnostic aid, for, if the patient is relieved of symptoms, if the ulcer disappears roentgenographically and if blood disappears from the stools, then the lesion is benign. Clinical experience, however, has demonstrated that in some cases of malignant gastric ulceration these criteria may seem to be satisfied but the lesion does not heal, it only seems to do so, for, as Schindler<sup>1</sup> has shown, the carcinomatous process may extend from the margin of the ulcer into the crater, obliterating it.

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\*In this paper the adjective "cardial" is used in reference to the cardia, in contradistinction to "cardiac," which is generally used in reference to the heart.

From the Division of Surgery, the Mayo Clinic

<sup>1</sup> Schindler, R. *Gastroscoy*, Chicago, University of Chicago Press, 1937, p. 257

The incidence of malignant changes in gastric ulcers has been stated to be from 10 to 20 per cent. Walton<sup>2</sup> said that the figures of Stewart<sup>3</sup> are now generally accepted. He concluded that in 9.5 per cent of cases chronic ulcer becomes carcinomatous and that carcinoma originates in a chronic ulcer in 17 per cent. Katsch,<sup>4</sup> however, reported an incidence of 20 per cent. Finsterer<sup>5</sup> found that in 532 cases of resection for gastric ulcer the ulcer was carcinomatous in 141, an incidence of "20.9 per cent." In 41 the lesion was diagnosed clinically as gastric ulcer, and the surgeon concurred in the diagnosis on macroscopic examination at the time of operation, histologic examination by a competent pathologist, however, revealed early carcinoma. In 55 cases gastric ulcer was diagnosed clinically, but at operation the surgeon and the pathologist were able to make a diagnosis of carcinomatous ulcer. Chamberlain,<sup>6</sup> in Moynihan's clinic, in a follow-up study of 216 patients treated for suspected benign gastric ulcer, found that 9.5 per cent of the group had

TABLE 1—*Roentgen Diagnosis in Seventy-Six Cases of High Gastric Lesions in Which Examination Was Performed in 1938 and 1939*

	Cases	Per Cent
Correct roentgen diagnosis	67	83
Unqualified correct diagnosis	54	71
Ulcerative lesion, unable to say whether benign or malignant	13	17
Incorrect roentgen diagnosis (lesion described as benign when malignant and vice versa)	7	9
Negative roentgen report	2	3

died of carcinoma of the stomach. Balfour<sup>7</sup> said that the subsequent death rate of patients operated on for duodenal ulcer is not greater than that of the general population of similar age and sex but that the subsequent death rate of patients operated on for gastric ulcer is three times as great as that of the general population. Gastric carcinoma is the most important single factor influencing life expectancy.

The possibility of healing a large gastric ulcer with a crater 1.5 cm or larger in diameter by other than surgical methods should be looked on with skepticism, for all such ulcers have a tendency to perforate.

2 Walton, J. Carcinoma of the Stomach, *Lancet* **1** 1101-1107 (May 16) 1936

3 Stewart, cited by Portis, S. A., and Jaffe, R. H. A Study of Peptic Ulcer Based on Necropsy Records, *J. A. M. A.* **110** 6-13 (Jan. 1) 1938

4 Katsch, cited by Hurst, A. F. Carcinoma of the Stomach, *Lancet* **2** 1455 (Dec. 18) 1937

5 Finsterer, H. Malignant Degeneration of Gastric Ulcer, *Proc. Roy. Soc. Med.* **32** 183-196 (Jan.) 1939

6 Chamberlain, D. Partial Gastrectomy for Gastric Ulcer, *Surg., Gynec. & Obst.* **45** 513-517 (Oct.) 1927

7 Balfour, D. C. Factors Influencing the Life Expectancy of Patients Operated on for Gastric Ulcer, *Ann. Surg.* **76** 405-408 (Sept.) 1922

Patients with such lesions usually have had clinical evidence of perforation of the ulcer either to the gastrohepatic omentum or to the pancreas, and many of them have had hemorrhages. When such lesions occur, surgical removal of the lesion affords the best chance of permanent cure and does it in a reasonably short time. This statement is true regardless of the age of the patient if his condition is otherwise satisfactory. Furthermore, surgical removal relieves the menace of fatal hemorrhage from the lesion or of an acute perforation which may require an emergency procedure for its closure. Of great importance is the removal of a lesion which may be malignant or may become so.

The risk of the operation for gastric ulcer should not exceed a maximum of 5 per cent, and it is possible to operate on a large series of patients with gastric ulcer with a mortality rate of considerably less than 5 per cent. In point of fact, in 215 resections performed at the Mayo Clinic in 1938 for benign lesions of the stomach and duodenum, the mortality rate was 2.8 per cent.<sup>8</sup> There were 43 partial gastrectomies for gastric ulcer, with a mortality rate of 2.3 per cent. The cases were selected carefully, and partial gastrectomy was performed only when the nature of the lesion and the condition of the patient warranted this procedure. The results of a properly chosen, properly performed operation for gastric ulcer are some of the best in surgical practice, for recurrence of the ulceration is rare. I have not seen recurrence of gastric ulcer or gastrojejunal ulcer after partial gastrectomy for gastric ulcer when half or more of the stomach has been removed. Recurrence of ulcer, in my experience, is rare when the gastric ulcer has been excised and gastroenterostomy performed.

In the experience of this clinic the large gastric ulcers are most frequently present along the lesser curvature of the stomach or slightly posterior to it. In Stewart's extensive series 3.5 per cent of the lesions occurred on the gastric side of the pyloric canal, 22.4 per cent were 1 to 2 inches (2.5 to 5 cm) from the pylorus, 34.1 per cent were 2 to 3 inches (5 to 7.5 cm) from the pylorus, 2.9 per cent were 3 to 4 inches (7.5 to 10 cm) from the pylorus, and 10.6 per cent were more than 4 inches (10 cm) from the pylorus. On reviewing 272 cases of chronic gastric ulcer in which operation was performed at the Mayo Clinic from Jan. 1, 1933, to Jan. 1, 1937, Clagett and I<sup>9</sup> found that 66.9 per cent of the ulcers were at or above the incisura angularis, 15

<sup>8</sup> Walters, W., Gray, H. K., and Priestley, J. T. Surgical Report for 1938 on Lesions of the Stomach and Duodenum, Proc. Staff Meet., May Clin. **14** 807-814 (Dec. 20) 1939.

<sup>9</sup> Walters, W., and Clagett, O. T. The Surgical Treatment of Chronic Gastric Ulcer. Review of Two Hundred and Seventy-Two Cases, Surg., Gynec. & Obst., to be published.

per cent were on the posterior wall and 1.5 per cent were on the greater curvature. The remainder were below the incisura angularis.

In several of the cases at the clinic the ulcer appeared on roentgen examination to be located very high on the lesser curvature, and for this reason it was thought that operative removal would be difficult, it was found at operation, however, that perforation of the lesion to the capsule of the pancreas had given an erroneous idea of the amount of stomach between the ulcer and the esophagus. In these cases there was actually much more uninvolved stomach than the roentgenogram indicated (table 1). On other occasions the early division of the gastrohepatic omentum at a very high level assisted in mobilizing the upper part of the stomach so that unusually high lesions could be removed without too great difficulty. Two observations led me to study a series of patients operated on for benign and malignant lesions situated midway between the incisura angularis and the esophagus or higher. These were as follows: (1) recognition of the fact that the roentgenologic appearance of a gastric ulcer can be so misinterpreted that necessary surgical procedures may be postponed and (2) a general impression that, although removal of a gastric ulcer is made more difficult when it is situated above the incisura angularis, the mortality rate from the operation is not increased appreciably. Finsterer<sup>10</sup> and Rieder<sup>11</sup> called the gastric ulcers situated in this region subcardial or juxta-cardial ulcers.

During 1938 and 1939 at the Mayo Clinic there were 42 cases in which operation was performed for benign lesions situated in the cardiac region, with 1 death, a mortality of 2.3 per cent (table 2). In 3 the lesions removed were polyps, in 2, diverticula, in 1, a leiomyoma, and in 1, a cyst. Local excisions were performed in 6 of these 7 cases, and partial gastrectomy was performed in 1. There were no deaths. Thirty-five patients who had cardiac benign gastric ulcers were operated on. Twenty-six partial gastrectomies were done for cardiac gastric ulcers, with 1 death, a mortality of 3.8 per cent. In 4 cases the ulcer was excised, and gastroenterostomy was performed. In 1 case excision of the ulcer was done, and in 4 cases gastroenterostomy was performed. In these 9 cases there were no deaths.

In 34 cases in which cardiac carcinoma was present surgical treatment was possible (table 2). In all but 1 gastric resection was performed, that is, partial gastrectomy in 28 and total gastrectomy in 5. In these 34 cases the mortality rate was 14.7 per cent. This mortality rate for operations for malignant disease in the upper part of the

10 Finsterer, H. Das cardianahe Magengeschwür, *Wien klin. Wchnschr.* **52** 394-400 (April 28) 1939.

11 Rieder, W. Chirurgische Behandlung des kardianahen Ulcus ventriculi, *Arch f klin Chir.* **196** 640-655, 1939, abstracted, *Internat. S. Digest* **29** 21-22 (Jan.) 1940.

stomach is in keeping with that following partial gastrectomy performed for all types of carcinomas of the stomach in the year 1938 at the clinic, which was 13.5 per cent (126 cases<sup>8</sup>)

The relative incidence of gastric lesions in the cardial portion of the stomach during 1938 and 1939 is of interest. There were 76 cardial lesions among the 542 gastric lesions for which operation was performed, an incidence of 14 per cent. In other words, 14 per cent of the patients with gastric lesions who underwent operation during the years 1938 and 1939 at the Mayo Clinic had lesions located in the cardial region. Finsterer,<sup>10</sup> in the course of 532 resections of the stomach for gastric ulcer, found 124 subcardial lesions, or 23.3 per cent.

TABLE 2—*Operative Procedures and Mortality Rates in Seventy-Six Cases of High Gastric Lesions in Which Operation Was Performed During 1938 and 1939 at the Mayo Clinic*

	Cases	Deaths	Mortality Rate, per Cent
All benign high gastric lesions	42	1	2.3
Benign gastric ulcers	35	1	2.8
Partial gastrectomy	26	1	3.8
Cautery excision or excision and gastroenterostomy	4	0	0
Simple excision	1	0	0
Gastroenterostomy	4	0	0
Miscellaneous benign lesions	7	0	0
Polyposis of stomach	3	0	0
Diverticula	2	0	0
Leiomyoma	1	0	0
Cysts of cardia (all excised except 1 cyst and 1 hemangioma)	1	0	0
High gastric carcinoma	34	5	14.7
Posterior Polya operation with or without modifications	15	2	13.3
Anterior Polya operation with enteroanastomosis	9	0	0
Total gastrectomy	5	2	40
Segmental resection of the stomach	2	0	0
Transgastric excision of lesion	2	1	50
Palliative posterior gastroenterostomy	1	0	0

Finsterer<sup>10</sup> and Rieder<sup>11</sup> both reported with favor on high gastric resection with removal of the ulcer whenever possible, and both advised the Kelling-Madlener type of subtotal gastrectomy, which allows the ulcer to remain in situ when it is situated too high to remove with safety. It is felt that by removal of the greatest acid-forming portion of the stomach more permanent cure is effected. In this procedure, which was originally proposed by Kelling<sup>12</sup> in 1918 and was described and brought into favor by Madlener<sup>13</sup> in 1923 and 1929, resection of the stomach below the ulcer is accomplished by anastomosis of the stomach to the duodenum by the Billroth I type of procedure. Fin-

<sup>12</sup> Kelling, G, cited by Finsterer<sup>10</sup>

<sup>13</sup> Madlener, M. Ueber Pyloroktomie bei pylorusfernem Magengeschwür, Zentralbl. f. Chir. 50 1313-1317, 1923, Ergebnisse der "palliativen" Resektion beim pylorusfernem Magengeschwür, ibid. 56 2694-2696, 1929



sterer<sup>10</sup> has reported anastomosis posterior to the colon of the end of the stomach to the side of the jejunum in the palliative resection when fixation of the duodenum might cause tension on the suture line. Lewisohn<sup>14</sup> stated that he does not favor the Madlener procedure, for the postoperative results of Madlener's operation when viewed in large numbers are unsatisfactory, the ulcer is not put at rest and gastric acidity is seldom sufficiently high preoperatively to require gastric resection for its reduction.

My impression coincides in some ways with these opinions. I believe that every gastric ulcer should, if possible, be removed by partial or subtotal gastric resection or, in less satisfactory conditions, by excision with or without gastroenterostomy. However, if the patient's condition is too poor to withstand resection or excision, gastroenterostomy is favored, for after gastroenterostomy for gastric ulcer a relatively high incidence of achlorhydria occurs, and healing of the ulcer frequently is obtained.<sup>15</sup> The mortality from such a procedure for chronic gastric ulcer in 228 operations, Eusterman and Balfour<sup>16</sup> stated, was 1.7 per cent, whereas in 540 cases of gastroenterostomy for acute, subacute and chronic gastric ulcer it was 3.9 per cent. Many of the patients for whom the operation was selected were poor surgical risks, or their condition was considered unfavorable for gastric resection, yet the results were good, for Eusterman and Balfour<sup>16</sup> found that 79 per cent of 100 patients with gastric ulcer for which gastroenterostomy was performed were well five years after operation, and 4 per cent were fairly well. Eusterman and Balfour stated that the operation protects against reactivation of the ulcer in more than 90 per cent of the cases and also protects against perforation and obstruction.

Clagett and I, in a study of 272 consecutive operations for gastric ulcer performed at the Mayo Clinic from Jan. 1, 1933, to Jan. 1, 1937, reported that 16 patients had undergone posterior gastroenterostomy, and 5 anterior gastroenterostomy with enteroenterostomy. Fourteen of these patients reported that they were in excellent health without distress of consequence after this type of operation, and 1 reported occasional mild distress. There was no report from 5 of the group. The average gain in weight was 15 pounds (6.8 Kg.). One hundred and sixty-two of the 272 patients underwent partial gastrectomy.

14 Lewisohn, R. Problems in the Surgical Treatment of Chronic Duodenal Ulcers, *Ann. Surg.* **111** 355-361 (March) 1940.

15 Walters, W. Gastric Acidity Following Operations for Gastric and Duodenal Ulcer. Its Effect on the Question of Partial Gastrectomy, *Ann. Surg.* **104** 585-593 (Oct.) 1936.

16 Eusterman, G. B., and Balfour, D. C. The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, pp. 469-471 and 505-514.

Gastrojejunal ulcer is very infrequent after gastroenterostomy for gastric ulcer. Thus, it seems that the good results and the excellent chance for relative achlorhydria from a simple operation with a low operative mortality may be preferable to a higher risk associated with resection when the ulcer cannot be removed. Jejunostomy is not favored because of the necessity of prolonged difficult treatment and the frequency of recurrence after closure of the opening.

As experience develops it will be found that more high gastric lesions will be found resectable. In this series of 35 cardial ulcers, partial gastrectomy was performed in 31 instances, or 88 per cent.

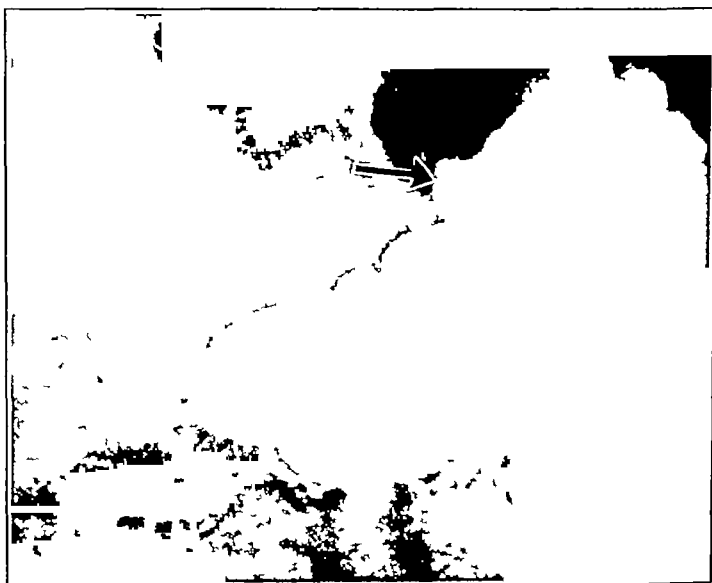


Fig 1—Gastric ulcer 2 cm. below the esophagus for which partial gastrectomy of the Hofmeister-Polya type was performed, with removal of the ulcer.

The illustrations and the abbreviated report of cases were selected not to demonstrate any special point but merely because they illustrate characteristic lesions of the type under consideration.

#### REPORT OF CASES

**CASE 1**—A man 60 years of age was admitted to the clinic Nov 1, 1939, complaining of anorexia, loss of 40 pounds (18.1 Kg) and constipation of nine months' duration. Roentgen examination of the stomach revealed a gastric ulcer 2 cm in diameter high on the lesser curvature (fig 1). On gastric analysis before operation the total acidity was 50 and the free acids 40 (Topfer's method). At operation an inflammatory gastric ulcer 2 cm. below the esophagus was found which had perforated into the gastrohepatic omentum. Partial gastrectomy of the posterior Hofmeister-Polya type was performed, with removal of three fourths of the stomach, including the gastric ulcer. The postoperative convalescence was uneventful. After operation the total acidity was 6, and there was no free acid.

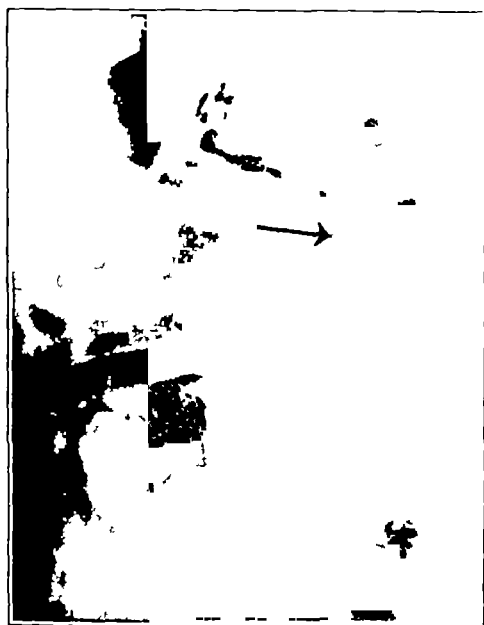


Fig 2—Gastric ulcer 3 cm below the cardia for which partial gastrectomy of the posterior Polya type was performed, with removal of four fifths of the stomach, including the ulcer



Fig 3—Extensive carcinoma of the stomach extending almost to the esophagus, for which partial gastrectomy of the posterior Polya type was performed, with removal of the lesion

CASE 2—A woman 64 years of age registered at the clinic on Aug 7, 1939, complaining of intermittent epigastric distress of ten years' duration and of chills, fever, nausea, vomiting and severe pain in the epigastrium and back of three weeks' duration. Roentgen examination of the stomach revealed an ulcer high on the lesser curvature of the stomach (fig 2). At operation an inflammatory gastric ulcer was found 3 cm below the esophagus, with a crater 1.5 cm in diameter. Partial gastrectomy of the posterior Polya type with removal of four fifths of the stomach, including the gastric ulcer, was done. The patient was well four months later.

CASE 3—A man 58 years of age entered the clinic Nov 21, 1939. He had had epigastric distress for twenty years and had lost 30 pounds (13.6 Kg) in the previous year. Roentgen examination of the stomach revealed extensive ulcerating carcinoma involving almost the entire stomach, which was probably inoperable (fig 3). Gastric analysis (Topfer's method) revealed a total acidity of 14 and



Fig 4—Huge ulcerating carcinoma involving all of the lesser curvature of the stomach, *a*, roentgenogram, *b*, carcinomatous ulcer removed at operation, partial gastrectomy of the posterior Hofmeister-Polya type was performed

no free acid. Partial gastrectomy of the posterior Polya type was performed, with removal of four fifths of the stomach for ulcerating perforating adenocarcinoma grade 2 (on a grading basis of 1 to 4). The growth measured 9 by 9 by 3 cm and extended almost to the esophagus. The convalescence was uneventful.

CASE 4—A man aged 63 years came to the clinic July 13, 1939, complaining of gastric distress, weakness and loss of 24 pounds (10.9 Kg) in the previous three months. Roentgen examination of the stomach revealed ulcerating carcinoma of the middle third and upper portion of the body of the stomach. The roentgenologist felt that operability was doubtful (fig 4a). Partial gastrectomy of the posterior Hofmeister-Polya type was done to remove four fifths of the stomach for a lesion which extended almost to the esophagus. The pathologist reported adenocarcinoma, grade 2, measuring 15 by 10 by 3 cm (fig 4b), this

was the largest carcinomatous ulcer ever removed at the clinic. The patient died after operation from bronchopneumonia

CASE 5—A woman aged 42 years entered the clinic Nov 27, 1939, on account of weakness and three gastric hemorrhages in 1938 and 1939. Roentgen exami-



Fig 5—Leiomyoma of the cardiac end of the stomach, *a*, roentgenogram, *b*, specimen removed by transgastric excision.

nation of the stomach showed a large polypoid tumor near the cardia (fig 5*a*). Gastric analysis revealed a value for total acidity of 84 and for free acid of 70. Excision through a transgastric approach revealed a leiomyoma, measuring 6 by 5 by 3 cm (fig 5*b*), which arose from the posterior wall of the cardiac area of the stomach. The convalescence was uneventful.

CASE 6—A woman, aged 52 years, was admitted to the clinic Sept 26, 1939, because of symptoms of peptic ulcer of six weeks' duration and hematemesis and melena of two weeks. Roentgen examination of the stomach revealed polyposis of the middle third and two polyps high in the stomach (fig 6). On gastric analysis total acidity was 10, and there was no free acid. Transgastric excision of multiple adenomatous polyps was done. The patient's convalescence was uneventful.

#### SUMMARY

Seventy-six, or 14 per cent, of the 542 gastric lesions for which operation was performed at the Mayo Clinic during 1938 and 1939 were found to be at or higher than a point midway between the angle of the stomach and the esophagus. In 35 of the 76 cases benign gastric ulcer

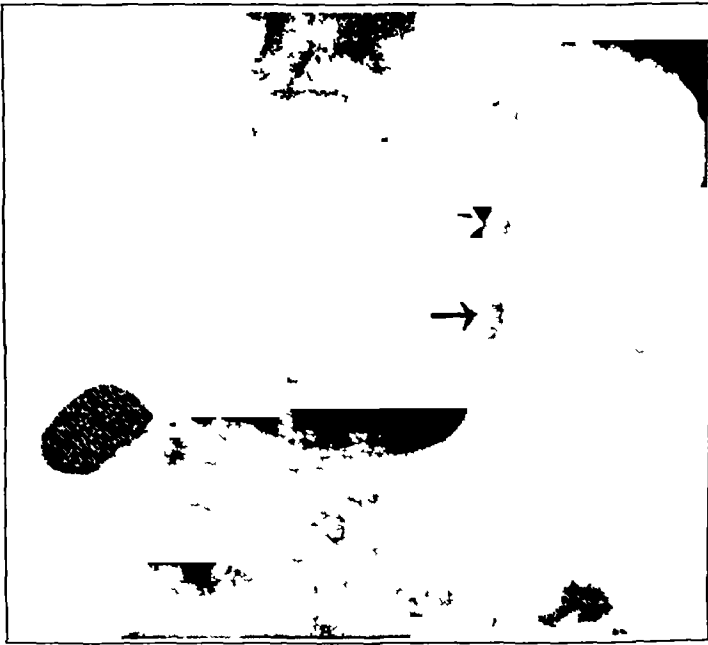


Fig 6—Polyposis of the stomach. There were two polyps in the vicinity of the cardia. Transgastric excision was performed.

was present. In 26 of the 35 cases of benign gastric ulcer situated high above the incisura angularis of the stomach partial gastric resection was performed, with 1 death. There were 34 cases of carcinoma in which the lesion was situated high above the incisura angularis of the stomach, some form of gastric resection (partial or total gastrectomy) was done in all but 1, with 5 deaths. In 7 cases miscellaneous benign lesions were removed by local excision, without mortality.

Frequently the high gastric lesion appeared higher in the roentgenogram than it actually was, because of foreshortening of the stomach proximal to it, caused by perforation of the ulcer onto the pancreas or into the gastrohepatic omentum. In most such cases ample stomach

could be found above the lesion for safe partial gastric resection after mobilization of the stomach and its perforating process and by high ligation of the gastrohepatic omentum

Partial or subtotal gastrectomy was preferred for the surgical treatment of cardial gastric ulcer. When the condition of the patient did not allow this, excision of the lesion with or without gastroenterostomy was favored. When the ulcer could not be excised with safety because of its proximity to the esophagus or because of the poor condition of the patient, gastroenterostomy was preferred, as a high incidence of relative achlorhydria and healing occurred after such a procedure. The Kelling-Madlener palliative gastric resection, in which the ulcer is not removed, has not been utilized by us.

The difficulty of differentiating a malignant from a benign ulcerative process in the cardial gastric region by roentgen examination was emphasized.

The material in this paper relative to cardial ulcers and to the follow-up study of cases has been assembled with the aid of Dr. William H. Cleveland, assistant surgeon, the Mayo Clinic.

## SUBDELTOID BURSTITIS

ALANSON WEEKS, M D

SAN FRANCISCO

Some six years ago, when Dr Dean Lewis was visiting me in San Francisco, I happened to bring up the subject of his system of surgery and how much he had included in it which was obsolete. When he asked me to be more specific, I called his attention to the fact I had discovered that the proper treatment of subdeltoid bursitis seemed to be unknown generally and that the old advice about diathermy, etc, was still given in his published work. I called his attention to the immediate relief of 90 per cent of this pain in the shoulder obtained by simple needling, which eases the tension in a dense, mesothelium-lined fibrous sac. He frankly stated that he had never heard of this treatment and told me that some day he would publish a one volume treatise on general surgery which would leave out everything obsolete and would include everything useful that one book would hold. I am still hoping for this volume.

Dr Lewis urged me to publish my method of treatment in the *International Clinics*, which I did in 1936,<sup>1</sup> and now, for his birthday issue of the *ARCHIVES*, I think it fair that this subject should be brought up again, because it is quite evident that this proper treatment for inflammation, whether traumatic or otherwise, of the subdeltoid bursa is not yet universally approved. This was particularly brought to my attention by the work of Ferguson,<sup>2</sup> as short a time ago as May 1938. On reading his resume, I again took up the subject with a number of my professional friends, especially orthopedic and general surgeons, and discovered that there is still some question about it.

The subdeltoid bursa may in some instances be connected with the shoulder joint, but because in all my cases of acute subdeltoid bursitis the symptoms are referable only to the bursa I have reason to believe that none of the bursae observed by me has been so connected. A great number of physicians now agree that 90 per cent of pains of any moment about the shoulder are due to an irritation within the subdeltoid bursa, and certainly the pain of an acute inflammation of this sac is so much more agonizing and incapacitating than any other that a simple pro-

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1 Weeks, A. Subdeltoid Bursitis (Acute), *Internat. Clin* 3 40-48 (Sept.) 1936

2 Ferguson, L. K. Shoulder Pain and Disability Due to Lesions of Subdeltoid Bursa and Supraspinatus Tendon. Five-Year Collective Review, *Internat Abstr Surg* 66 472-487, 1938, in *Surg, Gynec & Obst*, May 1938



cedure for its quick relief should be known universally. From the literature it is apparent that there have been so many misunderstandings about why the pain is relieved that I hope I am specific enough when I say that it is not the procaine hydrochloride or any other factor in the way of washing out the bursa between two needles or putting in a sclerosing solution that relieves the pain. It is simply relief of tension afforded by puncturing the firm-walled sac in numerous places with a needle. This amounts, of course, to the same thing as making an operation of it and laying open the sac with a knife, but it is so much simpler and can be done so easily in the office that there is little excuse for any delay or any added expense. Since my last report I have had some 40 patients in whom immediate relief was produced by needling only, and but 1 of these had any history of trauma. In other words, most patients with this condition have a history of infections connected with the nose, throat or teeth.

I first used this treatment for acute subdeltoid bursitis in 1908, purely as a diagnostic procedure, common then, because I suspected the presence of fluid in the region. The relief of pain was so instantaneous on aspiration of about 1 cc. of straw-colored fluid that I have applied it ever since, supposing it to be well known.

In 1913, Prof. J. M. Flint, of New Haven, Conn., suggested aspiration for acute traumatic bursitis but said nothing about this treatment for all forms of the disease. If he had done so, no doubt it would have been popularized long since, and much suffering might have been prevented.

Some of my friends who are orthopedic surgeons report that unless the calcium in the bursa has organized to the consistency of bone they are now treating the chronic forms of subdeltoid bursitis by thorough needling. This seems to change the blood supply and causes more rapid absorption of the salt. In other words, these surgeons find an operation unnecessary unless the deposit of salt has become bonelike. One of my friends told me last year that he had had, in the past three or four years, some 15 patients suffering from subdeltoid bursitis and that he never bothered any more to do the operation with the region under local anesthesia, because, of course, it is impossible to inject enough procaine hydrochloride into this painful sac to prevent some agony with the needling. He therefore now gives the patient a whiff of nitrogen monoxide and, as he expresses it, needles the bursa fanwise in all directions, from the outside well over into the region of the supraspinatus tendon. In no case has he failed to give immediate relief when the disease was acute. Of course, when a patient has suffered for two weeks with this agonizing disease, has been kept awake and has been unable to tolerate any motion whatever in the shoulder joint, there is bound to be some disability from the lack of use and from the outrage

to the associated nerves, but these disabilities are quickly forgotten when the acute agony has been relieved. All of the patients who have been under treatment and have suffered all of the old abuses, especially diathermy, say after treatment with diathermy their pain is increased a great deal. This, of course, is due to the heat, which causes more congestion and more tension in the tight sac.

In conclusion, I venture to say that every patient suffering from subdeltoid bursitis of the acute type, whether the sac contains calcium or not, will be relieved at once if the tension is removed by numerous punctures with a fair-sized needle, whether local anesthesia with procaine hydrochloride only or general anesthesia is used. Chronic conditions also will be relieved and the calcium absorbed after use of the same method, unless the salt has organized into bony hardness, in which case surgical removal is justified.

# OPERATIVE TREATMENT OF TRUE HERMAPHRODITISM

A NEW TECHNIC FOR CURING HYPOSPADIAS

HUGH H YOUNG, M D  
BALTIMORE

Hermaphroditism has interested the members of the medical profession since earliest days, but until recent years the clinical descriptions and the anatomic and microscopic studies were so inadequate that many early reports are not acceptable today

In 1924 I reported a case of true hermaphroditism which at that time was the ninth case acceptable by scientific standards. In 1937 I found that 11 additional accepted cases had appeared in the literature. Since then a case, previously questioned, has been shown to be a proved case of hermaphroditismus verus<sup>1</sup>. I wish to present my second case<sup>2</sup>.

## REPORT OF A CASE

An East Indian aged 20 came from Johannesburg, South Africa, on Dec 14, 1937, after having stopped to consult urologists in Italy, France and England. He was referred to me by Dr Vincent Vermooten. He had been brought up as a male and had no idea that he was anything else. He had normal male sexual desires but had never been able to have intercourse on account of a penile deformity. He had frequently masturbated.

Examination revealed a well developed, slight young man of masculine build, with a sparse growth of hair on the lips and face. There was an abundance of hair on the body and extremities. The breasts were typically male. There were a completely bifid scrotum and a penis of fair size, drawn backward in the scrotal cleft by a pronounced chordee. The urinary meatus was present between the halves of the bifid scrotum (fig 1). There was a furrow on the ventral surface of the penis, covered with mucous membrane. The right side of the scrotum contained a well developed, apparently normal testis and epididymis. On the

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From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital

1 J F Gudernatsch (*Am J Anat* 11 267, 1911) should be credited with a case of hermaphroditismus verus. The case was excluded by B Kwartin and J A Hyams (*J Urol* 18 363, 1927), but a careful study of Dr Gudernatsch's documents shows conclusively, I believe, that his case is entirely acceptable. The total number of acceptable cases, up to the date of publication of my "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases" (Baltimore, Williams & Wilkins Company, 1937) is therefore 21, instead of 20.

2 This case was reported to the American Urological Association at its annual meeting in Quebec, Canada, on June 29 1938.

left side there was a large reducible scrotal inguinal hernia (fig 1) No testicle could be felt On rectal examination the outlines of the prostate were indefinite Beneath the rectum was an unusual oblong soft structure Vigorous massage did not produce any prostatic fluid



Fig 1—Condition before operation The penis is concealed between the halves of the scrotum

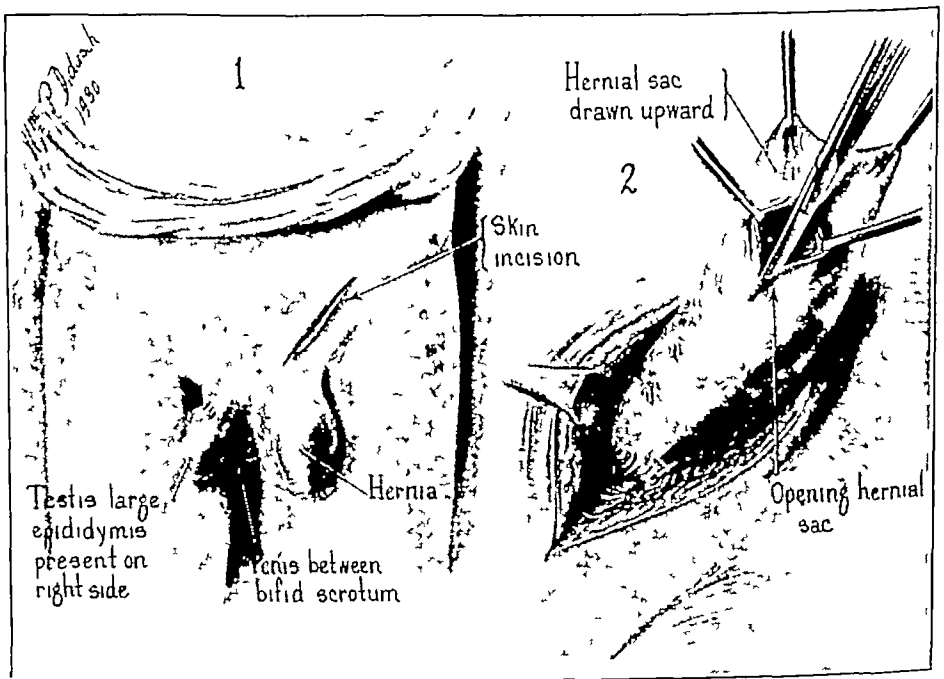


Fig 2—Operation for the hernia on the left side 1, cutaneous incision, 2, the sac delivered and opened

A cystoscope passed easily into the bladder, which was normal As the instrument was drawn out, Dr Lloyd G Lewis was able to make out an opening into which the cystoscope could be introduced It was evident that the cystoscope

was in a vagina, at the upper end of which the cervix uteri and the os were visible. A solution of 12 per cent sodium iodide was introduced into the cavity, and a uterogram was obtained. Study of the film showed that the fluid extended out into what appeared to be a fallopian tube on the left side.

Roentgenograms of the spine and pelvis showed the bones to have male characteristics.

A determination of urinary estrogen showed no increase (only 4 rat units per twenty-four hour specimen).

A tentative diagnosis of hermaphroditism was made. The case was apparently similar to that reported by me in 1924<sup>3</sup>.

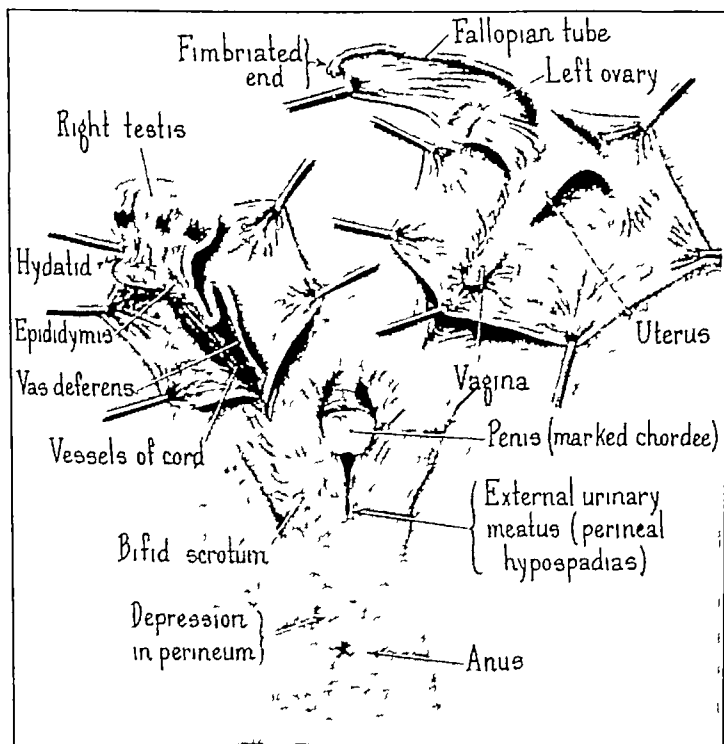


Fig 3—After opening the hernial sac on the left side, the uterus, tube and ovary were discovered. At a second operation, several weeks later, the scrotum was opened on the left side, and the testicle and the abnormal epididymis were discovered.

On December 18 a left inguinal hernia was exposed through an oblique incision in the groin (fig 2). After freeing and opening of the sac a small uterus, a fimbriated left tube and a gonad were seen. The gonad measured 1.5 by 1.6 cm. The tube measured 10 cm in length. The uterus was 2 cm in diameter and 4 cm long and was attached by a stalk, undoubtedly a vagina, that disappeared in the

<sup>3</sup> Young, H. H. Bull. Johns Hopkins Hosp. 35:165, 1924. Young, H. H., and Davis, D. M. Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 119.

pelvis beneath the peritoneum. Springing from the other cornu of the uterus was a small cord that was attached to the peritoneum (fig 3). The gonad was peculiar in appearance. There was no evidence of ovulation, and the structure was different from the normal ovary. Attached to the right cornu of the uterus was a fibrous band that was adherent to the hernial sac. The broad ligament, with a normal blood supply, was present. The question arose whether the gonad was an ovary or a testicle. It was impossible to say definitely what the structure was, but it was small and apparently functionless, and as the patient was distinctly masculine in figure, habits and desires it was decided to remove the uterus, the tube and the gonad (fig 4). The hernial sac was dissected downward, so that the vagina was isolated

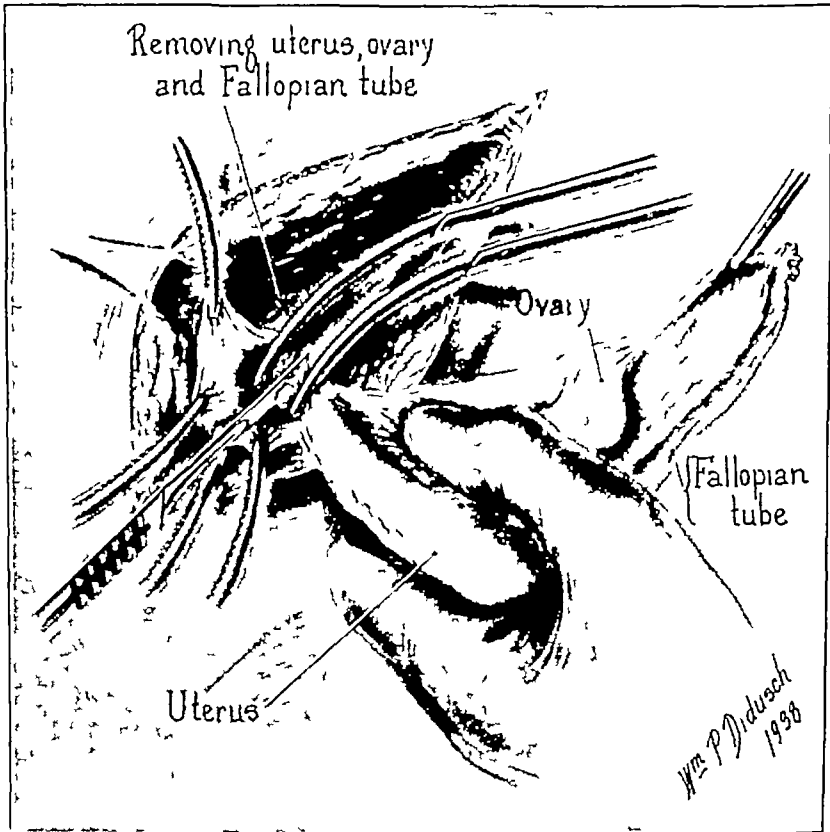


Fig 4—Removal of uterus, tube and ovary after division of the vagina through an incision in the left groin

outside the peritoneum. It was clamped, divided and ligated. The uterus, tube and gonad were removed in one piece with the hernial sac. The edges of the peritoneum were picked up and approximated with chromic catgut suture of the purse-string type. Dr Lewis then freed the fascia of the external oblique muscle and completed the operation for hernia repair according to the principles of Halsted.

A plastic operation to straighten the penis was carried out by me. The incision extended backward so as to excise the very pronounced congenital chordee. To liberate the penis completely it was necessary to carry out this excision of fibrous tissue down to and between the corpora cavernosa and to free the lower end of the urethra from its attachments and transplant it backward in the perineum. By this technic, which I have carried out in other cases, a large wound was

produced that completely liberated the penis after the skin had been divided on each side (fig 5). The edges of the skin were then approximated with silver wire sutures that passed through the skin and the septum of the corpora. When tied, this suture drew the two edges of the skin together against the corpora, thus producing a furrow that prevented the formation of a fibrous cord. The penis was held forward against the abdomen by means of a suture through the glans in which a rubber band was interposed to make traction. The wound was covered with silver foil, and a sterilized sea sponge was placed over the paper covering the foil to make gentle pressure. A catheter was not inserted, the patient was allowed to void naturally.

The patient could not void after the operation, and a catheter was introduced and left in place. The wounds healed by first intention. When he was discharged on the twentieth day the chordee had been completely corrected, and the penis

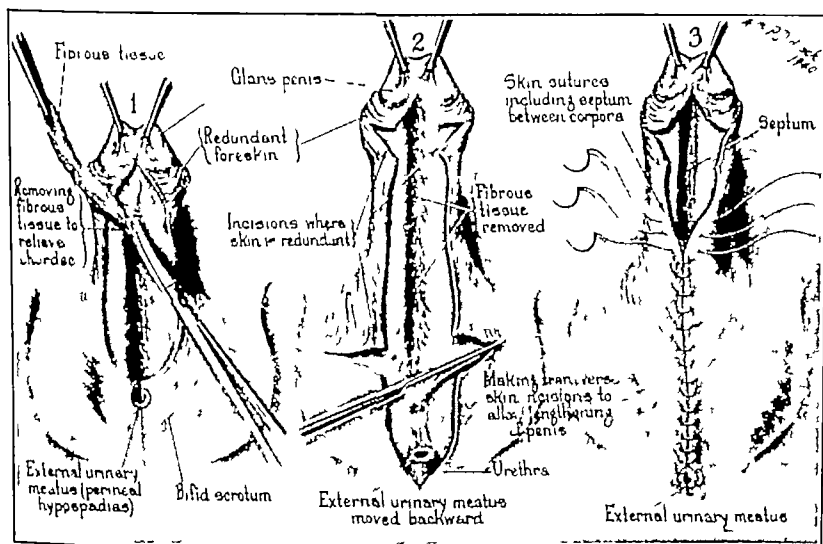


Fig 5—Young's operation for hypospadias (first stage). Note the complete removal of the fibrous cord in 1, transverse incisions through the skin where it is redundant in the foreskin and scrotum, 2, posterior displacement of the urinary meatus and triple suture to approximate the skin and draw it to the septum between the corpora cavernosa, 3.

was straight. He was voiding through the urogenital sinus, which opened far back in the perineum. The result of the hernia operation was apparently excellent.

On March 2, 1938, a second operation was carried out with the patient under nitrogen monoxide and ether anesthesia. It consisted of aspiration of material from the testicle and epididymis by Dr. Lewis for spermatozoa. The result being unsatisfactory, an incision was made in the right side of the scrotum, and the testicle was exposed after the tunica vaginalis had been opened. The testicle was larger than normal, measuring 5.3 by 3 by 2.8 cm. The surface was irregular and mottled, similar to the testicle in my other case of hermaphroditismus verus. The epididymis was very abnormal (fig 3). It did not lie in the usual position next to the testicle. The globus major was attached to the testicle by a thin mass of tissue about 7 mm long. The body of the epididymis was much smaller and

longer than normal. The globus minor was long and thin. The vas appeared normal. An incision was made in the tunica vaginalis, and through it testicular tissue extruded. This was increased by making pressure on the gland, and by means of scissors a sufficient amount of tissue was removed for biopsy. (This

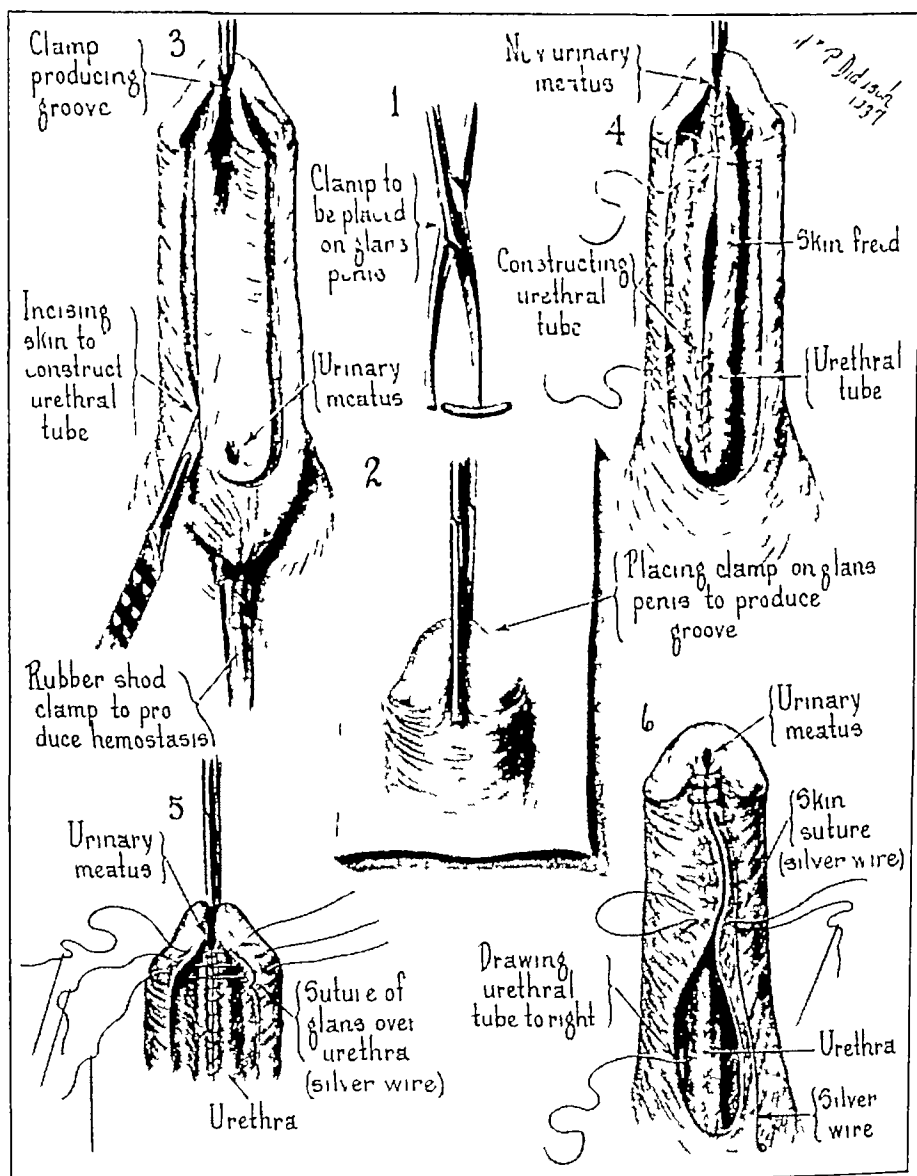


Fig 6—Young's modification of the Thiersch plastic operation to form a urethra. 1, clamp used on the glans, 2, clamp in place, 3, cutaneous incisions, 4, formation of the urethra, 5, suture of the glans over the urethra, 6, completion of closure of the skin with vertical mattress sutures.

method is preferable to excising a piece of testis). The wound was then closed by sutures of fine catgut.

The next procedure was to provide drainage through the perineum back of the urinary meatus in the mid perineum. I decided not to attack the vagina. A new urethra was then formed by the method illustrated. The incision on the right side was about 8 mm from the midline, and on the left 15 mm (fig 5).



The incision was carried downward to include the glans. The cut edges of the skin were approximated and inverted by a continuous fine catgut suture with a Duloc needle (fig 6, 4). The skin was then approximated with my vertical mattress suture of very fine silver tied over a thread of silver wire (fig 6, 5 and 6). (I often use a very delicate rubber tube instead of the piece of silver wire.) Examination showed a good deal of tension of the skin along the last 25 cm of the penis. I therefore made an incision along the dorsum for this distance and at the upper end carried an oblique incision on each side (fig 7). With the skin freed on each side, no difficulty was experienced in drawing the upper half of the Y down into the lower part of the wound and suturing it there so as to form a V. This procedure, which I have carried out in a number of cases, is

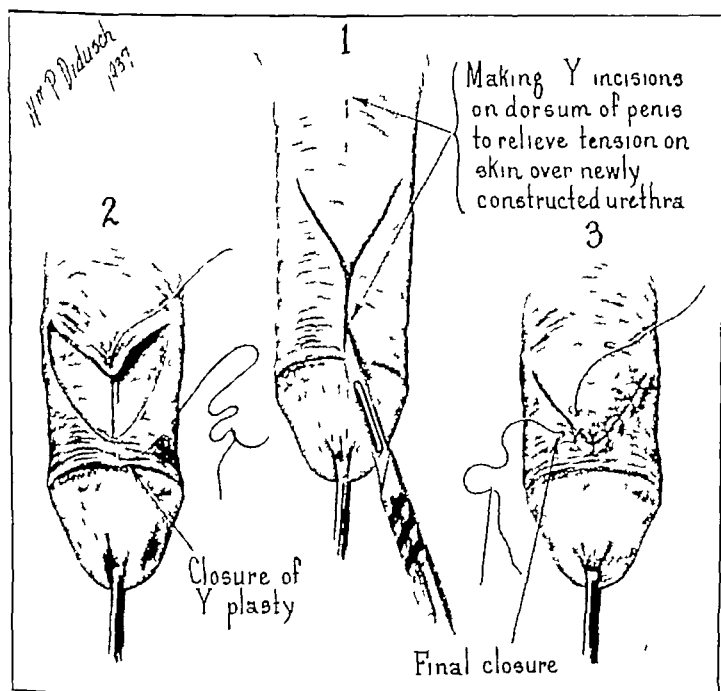


Fig 7—Y-V plastic operation for the dorsum of the penis, to relieve tension

very effective in combating tension of the penile skin resulting from the urethral plastic procedure. It also has the effect of drawing the dorsum upward and helping to correct any tendency to chordee. (In some cases I find it necessary to use the Y-V plastic procedure twice along the dorsum [fig 7, 1].)

The patient remained in the hospital four weeks. The healing was per primam intentionem, except at one point just back of the glans, where a small fistula formed, and another place nearby. The penis was straight and of normal length. Most of the urine still passed through the perineal urethrotomy wound, through which the catheter emerged.

On June 1 the perineal mucocutaneous fistula was excised, a small catheter was inserted, and the tissue was drawn tight around it, with the hope that when it was removed the urethrotomy fistula would close. The fistulas, one the size of a pinpoint, near the meatus, and the other about 2 mm in diameter, 5 mm

behind the meatus, were present. These were dissected out, the internal orifice was closed with a purse-string suture of fine catgut and the edges of the skin were approximated with vertical mattress sutures of silver tied around the silver wire on each side. The meatus was enlarged by an incision along its roof that divided a valvelike projection. This operation was not entirely successful.

The patient returned a little later, and the previous operation was repeated to close the fistulas that had recurred. The operation was successful in closing the larger fistula, but a minute opening remained immediately behind the meatus in the glans, through which only a most delicate intestinal needle could be passed, and urine continued to come through the original urethrotomy wound. The urethra was dilated. A catheter was passed from the meatus into the bladder, and the perineal mucocutaneous fistula was excised and closed, but it broke down.

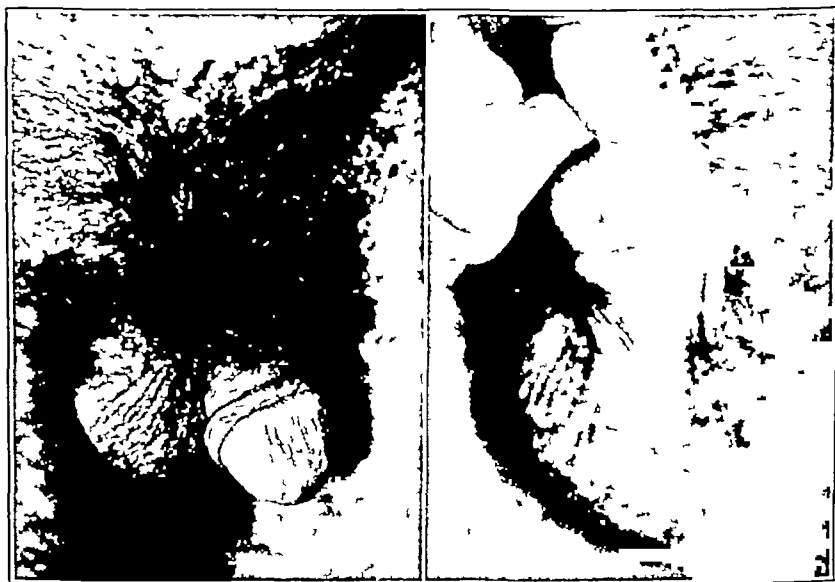


Fig 8—Final result after the operations to cure the chordee and construct a urethra from the perineum to the meatus. The patient voids normally through the new glandular urethra.

On August 10 the patient reentered the hospital. A suprapubic incision was made to drain the bladder. The perineal fistula was then excised and closed in layers. The very minute fistula in the glans was again closed as before.

The pinpoint opening recurred, and, as all attempts to close it had failed, the small bridge of tissue (only 3 mm wide) between the meatus and the fistula was incised with scissors, thus enlarging the meatus backward but causing no defect and completely removing the fistula.

The patient was finally discharged on October 4. The operative result was very satisfactory (fig 8). The penis was straight. The urinary meatus extended only a little farther back than normal. No fistulas were present. Urine was voided freely and in a good stream. The right testis was in the normal position. The left inguinal hernia apparently had been cured. The patient reported that he had had sexual intercourse frequently. Libido was normal, erections were straight and ejaculation was normal and entirely satisfactory. On rectal examination a soft tubelike structure 4 cm long could be felt immediately beneath the

rectal wall (remaining portion of the vagina) Beneath this a body, apparently the prostate, about two-thirds the normal size, was palpable The outlines of the seminal vesicles were indefinite The fluid obtained by prostatic massage showed many leukocytes and some lecithin cells

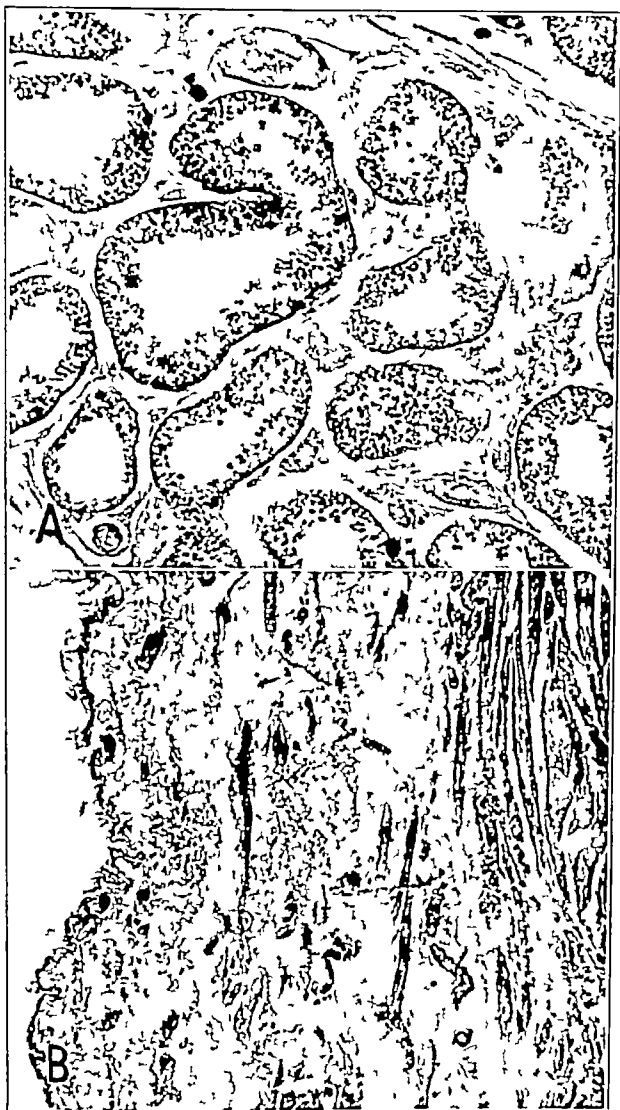


Fig 9—Photomicrographs of (A) testicle and (B) uterus

*Pathologic Report*—Section of the fallopian tube showed a small central canal Cross section of the ovary showed yellowish white translucent tissue No follicles were seen. Section of the uterus showed a small cavity that extended downward into the attached portion of the vagina that had been excised

Microscopic study of the sections of the uterus, the vagina and the fallopian tube (figs 9 and 10) showed structures typical of these organs. The stroma of the gonad (ovary) was made up of a large number of spindle-shaped cells and fibers arranged in whorls, perfectly typical of ovarian stroma (fig 10A). No



Fig 10—Photomicrographs of (A) ovary and (B) fallopian tube

definite follicles were seen. In some places there were circular masses of cells suggesting granulosa cells. Surrounding these the stroma cells were concentrically arranged, suggesting the theca interna. Many areas of cylindric calcified so-called psammoma bodies were observed, but no mature follicles and no bodies representing corpora lutea were seen.

Histologic examination of the tissue removed from the right testicle (fig 9 A) showed many seminiferous tubules that were normal in appearance. Every stage of spermatogenesis was seen. Sertoli cells were recognized among the larger primary spermatocytes. The interstitial tissue was rather scant, but the cells seemed normal.

The patient has reported to me by letter many times since he left here. On board ship he frequently had intercourse and unfortunately contracted gonorrhea, which was treated in London, England, with success. After he returned to South Africa a small right inguinal hernia that had developed was cured by operation by Dr Vincent Vermooten. On March 1, 1940, the patient reported by letter that he was normal in every respect.

#### COMMENT ON THE OPERATIVE TREATMENT

In this case the chordee and the hypospadias were virtually cured by two operations, after which there remained only minute fistulas, two of which were easily cured. The third, in the membranous skin of the glandular urethra, did not close and was simply done away with by enlarging the meatus. The procedures that I employ are much more simple than those usually advocated. The first operation, to cure the chordee, is much more extensive than has been previously employed. Instead of using the various Heineke-Mikulicz procedures, I go in boldly in the median line and excise the cicatricial tissue that produces the chordee, going down to and between the corpora cavernosa until the penis is completely freed of all restricting bands. In order to add to the effectiveness, the urinary meatus is transplanted much farther back in the perineum, thus adding to the freedom of the corpora cavernosa. The use of the triple stitch of fine silver wire that draws the skin in between the corpora prepares the way for the next operation. Abundant skin is afforded by the plan followed, *i. e.*, to divide the skin on each side of the incision at points where it is redundant, *viz.*, near the lower end in the prepuce and in the scrotum. At the second operation abundant skin for the modified Thiersch plastic operation is present, but to insure absolute lack of tension the Y-V plastic operation that I employ on the dorsum is completely effective. A simple, continuous, very fine plain catgut suture with the Duloc needle is then employed to turn in the skin to form a urethra. The newly made urethra is completely covered by drawing together the lateral edges with my vertical mattress suture of extremely fine silver wire that can be tied in a knot over either silver wire or a delicate rubber tube. This suture approximates broad surfaces, and the silver wire, being antiseptic, is an ideal suture material. Two or three minute fistulas usually remain to be closed after this operation. The technic employed is the same, fine plain catgut is used to turn in the urethra and a vertical silver wire mattress suture tied around a rubber tube to close the defect. Since I have adopted these methods I have almost always succeeded in com-

pletely curing the chordee and furnishing a urethra out to the glans penis, so that the patient has had normal urination and also normal sexual powers. I have entirely discarded the many complicated plastic operations described in the literature.

The case of hermaphroditismus verus that I have described belongs to group E in the classification that I made in my book, "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases." The case is identical with my first one except that the ovary had not gone so far toward complete development and the ovulation was not complete. The patient, however, was just as masculine as in my first case, and his sexual powers were normally male. The operations to cure the hernia, remove the female organs, eradicate the chordee and form a new urethra to the glans penis were entirely successful in both cases.

## EFFECT OF CHOLECYSTOGASTROSTOMY ON CINCHOPHEN-PRODUCED ULCER IN DOGS

HENRY SWAN, M D

DENVER

The role played by the digestive juices in the causation of peptic ulcer has long been under investigation. The acid "gastric chyme" has been studied by a variety of methods, and from the results obtained many investigators have delegated to it the role of villain in the drama of the pathogenesis of ulcer. From this point of view, interest was aroused in possible mechanisms or substances which might normally "protect" against ulcer formation. Among these, attention has been centered on the alkaline digestive juices—the succus entericus, the pancreatic juice and the bile. Attempt has been made to evaluate the "protective" qualities of these secretions *in toto*, singly and in various combinations.

Most previous work has been done by means of the Mann-Williamson preparation, whereby "duodenal drainage" is instituted and then single or combined alkaline juices are reshunted to the upper part of the intestinal tract in an attempt to evaluate their "protective" action. Recently, however, a new method of producing chronic gastric ulcers experimentally in dogs was discovered by Churchill and Van Wagoner.<sup>1</sup> This is accomplished by daily administration of old cinchophen, which results in a very high incidence of gastric ulcers closely simulating those seen clinically in man. This method has the advantage of not introducing a surgical procedure or altering the normal continuity of the gastrointestinal tract in the production of the ulcers.

This newer technic suggested itself to me as another method whereby the "protective" influence of the alkaline juices might be evaluated, and this paper is a report of the experimental investigation of one of these juices, *i. e.*, the bile.

From the Department of Pathology, the University of Colorado School of Medicine and Hospitals

<sup>1</sup> Churchill, T. P., and Van Wagoner, F. H. Cinchophen Poisoning. *Proc. Soc. Exper. Biol. & Med.* **28**: 581, 1931. Van Wagoner, F. H., and Churchill, T. P. Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning. Preliminary Report. *J. A. M. A.* **99**: 1859 (Nov. 26), 1932.

## REVIEW OF LITERATURE

The attempt to produce chronic ulcer in experimental animals has long engaged the attention of many investigators throughout the world, and a variety of technics have been involved which produced ulcerations in various laboratory animals. These experiments have been reviewed in detail by McCann.<sup>2</sup> Although a great variety of methods produced ulcerations in many different animals, it was apparent that none of these technics gave consistent results, that the ulcers were chiefly acute lesions which tended to heal rapidly and hence were in no wise similar to the chronic indurated lesion observed in man and that only certain animals, especially dogs, have gastric mucosa which behaves enough like that of the human being to make them valuable as experimental subjects. That a great variety of factors may initiate gastric or duodenal ulceration seems clear from these experiments, but the real problem, "the circumstance that it usually so obstinately refuses to heal," as Cohnheim stated in 1880, was not approached.

In 1923, however, Mann and Williamson<sup>3</sup> demonstrated a method whereby chronic indurated ulcers might be produced in a high percentage of dogs. This procedure, anastomosis of the stomach to the jejunum with "drainage" of the intervening duodenum into the lower part of the small bowel, had been previously done in effect by Bickel<sup>4</sup> in 1909 and by Langenskiöld<sup>5</sup> in 1914, but these authors had not followed up their observations, and their conclusions were not generally adopted. After the clear demonstration by Mann and Williamson<sup>3</sup> of the value of this technic an era of intense experimentation was begun. Morton<sup>6</sup>, McCann,<sup>7</sup> Gallagher and Palmer,<sup>8</sup> Jenkins and Palmer<sup>9</sup> and Matthews

2 McCann, J. C. Experimental Peptic Ulcer, *Arch Surg* **19** 600 (Oct) 1929.

3 Mann, F. C., and Williamson, C. S. The Experimental Production of Peptic Ulcer, *Ann Surg* **77** 409, 1923.

4 Bickel, A. Beobachtungen an Hunden mit extirpiertem Duodenum, *Berl klin Wchnschr* **46** 1201, 1909.

5 Langenskiöld, F. Ueber die Widerstandstahigkeit einiger lebender Gewebe gegen die Einwirkung erweisspaltender Enzyme, *Skandinav Arch f Physiol* **31** 1, 1914.

6 Morton, C. B. Observations on Peptic Ulcer. I. A Method of Producing Chronic Gastric Ulcer, a Consideration of Etiology, *Ann Surg* **85** 207 and 879, 1927, III Healing of Experimentally Produced Ulcer After Gastro-Enterostomy, *ibid* **85** 729, 1927, V Findings in Experimentally Produced Peptic Ulcer. Etiologic and Therapeutic Consideration, *ibid.* **87** 401, 1928.

7 McCann, J. C. Control of Acidity, *Am J Physiol* **89** 483, 1929, footnote 2.

8 Gallagher, W. J., and Palmer, W. L. Experimental Jejunal Ulcer. Relative Importance of Mechanical and Chemical Factors, *Proc Soc Exper Biol & Med* **30** 468, 1932.

9 Jenkins, H. P., and Palmer, W. L. Studies on Experimental Jejunal Ulcers, *Proc Soc. Exper Biol & Med* **28** 935, 1931.



and Dragstedt,<sup>10</sup> to mention only a few of the investigators, confirmed the value of the method. It was felt by most of these authors that two factors are important in the establishment of the ulcers: (1) the acid gastric chyme acting unneutralized on the jejunal mucosa and (2) the mechanical force of the ejected stream of chyme impinging against the jejunal wall.

This work stimulated an interest in the protective action of the duodenal juices and gave an experimental method whereby they might be studied. Bile has received particular attention in this regard.

The composition of bile varies considerably in different species and within the same species. However, its  $p_{H}$  has been stated by Horrall<sup>11</sup> to vary between 5.7 and 7.86, while that of hepatic bile was said by Jones<sup>12</sup> to lie between 7.4 and 8.5. Boldyreff<sup>13</sup> found the alkalinity of bile to be equivalent to only 0.05 per cent sodium carbonate. However, despite its low actual alkalinity, it has been felt that its buffering capacity is high.

It was first noticed by Hooper and Whipple<sup>14</sup> that a large percentage of dogs with external biliary fistulas had peptic ulcers. Thus it seemed that loss of bile alone from the duodenum resulted in a fair incidence of duodenal ulcers. Kapsinow<sup>15</sup> criticized the interpretation of this work on the basis that infection ascending the fistulous tract might be an important factor. He therefore performed cholecystonephrostomy on 43 dogs, in 17 of which chronic duodenal ulcers developed. Neumann and his co-workers<sup>16</sup> diverted the bile to the ileum and produced 5 ulcers in 7 dogs. They repeated the experiment on 2 additional series and got similar results. Weiss and Gurriaran<sup>17</sup> observed one ulcer in 3 fistulous

10 Matthews, W. B., and Dragstedt, L. R. The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55** 265, 1932.

11 Horrall, O. H. Bile: Its Toxicity and Relation to Disease. Chicago, University of Chicago Press, 1938.

12 Jones, K. K. Comparison of Buffer Value of Bile and Pancreatic Juice Secreted Simultaneously. *Proc. Soc. Exper. Biol. & Med.* **28** 567, 1931.

13 Boldyreff, W. The Self Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, *Quart. J. Exper. Physiol.* **8** 1, 1915.

14 Hooper, C. W., and Whipple, C. H. Bile Pigment Output and Diet Studies, *Am. J. Physiol.* **40** 332, 1916.

15 Kapsinow, R. The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, *Ann. Surg.* **83** 614, 1926.

16 Neumann, F., Demoor, P., and Deloyers, L. Contributions a l'etude de la pathogenie des ulcères gastroduodénaux. Derivation exclusive de la bile dans l'iléon terminal, *Compt. rend. Soc. de biol.* **105** 890, 1931.

17 Weiss, A. G., and Gurriaran, G. Ulcères chroniques gastroduodénaux expérimentaux créés par la dérivation des sucs alcalins duodénaux. *Bull. et mem. Soc. nat. de chir.* **36** 6, 1930.

dogs, Owings and Smith<sup>18</sup> two in 5, and Graves<sup>19</sup> one in 8. Bachrach and others<sup>20</sup> observed two ulcers in 15 dogs. Berg, Johnston and Jobling<sup>21</sup> observed the incidence of ulcer in Rous-McMaster fistulous dogs to be 77 per cent. These and other demonstrations indicated that "exclusion of the liver," by whatever means, is followed by the occurrence of duodenal ulcers in a percentage of the animals. However, this percentage varied greatly in the hands of different workers and with different technics. Moreover, it was not clear whether the lesions arose because of the lack of bile as a "protective" substance in the duodenum or were associated with the profound metabolic changes which occurred in the fistulous dogs. Berg and his associates found that a larger percentage of dogs receiving poor diet and living in a poor environment had ulcers than of dogs with a better hygienic regimen, and Ivy<sup>22</sup> and others have also emphasized that cachexia is an important predisposing factor in experimental ulcer.

Blanck<sup>23</sup> stated that in all of 5 dogs with biliary fistula duodenal ulcers were obtained, while of 3 others which were refed the bile obtained from the fistula only 1 had an ulcer. Bachrach and his co-workers<sup>20</sup> have criticized this work, however, pointing out that the series was small and the time of survival too short. These authors were able to obtain only two duodenal ulcers in 15 fistulous dogs, and Graves<sup>19</sup> pointed out that Rous and McMaster, Elman, and Puestow found no ulcers in their experiments with fistula.

To attempt to evaluate the actual local protective value of bile, Ochsner and his associates<sup>24</sup> made a gastric pouch and anastomosed the jejunum to the pouch. Ulcers formed in the adjacent jejunum in 85 per cent of cases. If they also anastomosed the gallbladder to the pouch only 39 per cent of the animals had ulcers. DeBakey<sup>25</sup> performed pyloric exclusion with anterior gastroenterostomy in 20 dogs. Fifty per cent had jejunal ulcer. If he also diverted the bile by anastomosing

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18 Owings, J. C., and Smith, I. H. Experimental Production and Cure of Jejunal Ulcers, *Proc Soc Exper Biol & Med* **29** 837, 1932.

19 Graves, A. M. Combined and Separate Effects of Bile, Pancreatic Secretion and Trauma in Experimental Peptic Ulcer, *Arch Surg* **30** 833 (May) 1935.

20 Bachrach, W. H., Schmidt, C. R., and Beazell, J. M. The Relation of Bile and Pancreatic Juice to Duodenal Ulcer in Dogs, *Proc Soc Exper Biol & Med* **40** 322, 1939.

21 Berg, B. N., Johnston, A., and Jobling, J. W. Duodenal and Gastric Ulcers in Dogs with Biliary Fistulae, *Proc Soc Exper Biol & Med* **25** 334, 1928.

22 Ivy, A. C. Studies on Gastric and Duodenal Ulcer, *J A M A* **75** 1540 (Dec 4) 1920.

23 Blanck, E. E. Peptic Ulcer, *Surg, Gynec & Obst* **61** 480, 1935.

24 Ochsner, A., Gage, M., and Hosoi, K. The Relationship of Peptic Ulceration to Gastric Chemism, *Proc Soc Exper Biol & Med* **31** 1260, 1934.

25 DeBakey, M. E. Peptic Ulceration. The Relative Protective Value of the Alkaline Duodenal Juices, *Arch Surg* **34** 230 (Feb) 1937.

the common duct to the ileum, 90 per cent had ulcers. These authors concluded, therefore, that bile has a definite local protective value. That its presence alone in the jejunum of a Mann-Williamson dog is inadequate to protect against ulcer formation was shown by Graves, who did "duodenal drainage" and then anastomosed the common duct to the jejunum. In 5 of his 6 animals the usual ulcers developed. Likewise, Neuman and his associates,<sup>26</sup> who performed a similar operation except that they anastomosed the gallbladder to the jejunum, obtained ulcers in 2 of 5 dogs.

The introduction by Van Wagoner and Churchill in 1932 of the cinchophen method of producing gastric ulcer in dogs has opened a new avenue of approach in the experimental study of ulcer. By feeding old cinchophen to dogs over a long period, chronic indurated ulcers, located chiefly in the stomach, were produced in a large percentage of animals. This work was soon confirmed by Bollman and Mann<sup>27</sup> and Barbour and Fisk.<sup>28</sup> Early gastritis occurs, which clears up, leaving a single or, rarely, a double chronic indurated lesion almost invariably situated on the lesser curvature of the stomach, just above the pylorus. Schwartz and Simonds<sup>29</sup> observed that chronic ulcer was developed by this method in cats and dogs but not in rabbits and guinea pigs. Churchill and Manshardt<sup>30</sup> found that gastric ulcers resulted even if the drug was administered into an isolated loop of intestine. Hanke<sup>31</sup> found that use of the subcutaneous route resulted in ulcerations in the stomachs of cats. Stalker, Bollman and Mann<sup>32</sup> stated that ulcer will result

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26 Neumann, F., Demoor, P. and Deloyers, L. Contribution a l'etude de la pathogenie des ulcres duodenaux. Derivation des sucs duodenaux et pancreatiques dans l'ileon terminal, *Compt. rend. Soc. de biol.* **105** 892, 1931.

27 Bollman, J. L., and Mann, F. C. Experimental Production of Gastric Ulcers, *Proc. Staff Meet., Mayo Clin.* **10** 580, 1935.

28 Barbour, H. G., and Fisk, M. E. Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, *J. Pharmacol. & Exper. Therap.* **48** 341, 1933.

29 Schwartz, S. O., and Simonds, J. P. Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog, *Proc. Soc. Exper. Biol. & Med.* **32** 1133, 1935.

30 Churchill, T. P., and Manshardt, D. D. Experimental Production of Gastric and Duodenal Ulcers in Dogs in Cinchophen Poisoning, *Proc. Soc. Exper. Biol. & Med.* **30** 825, 1933.

31 Hanke, H. Ueber experimentelle akute Atrophylgastritis als Erscheinungsform einer vorwiegend toxisch bedingten Gastritis. *Beitr. z. path. Anat. u. z. allg. Path.* **94** 313, 1934.

32 Stalker, L. K., Bollman, J. L., and Mann, F. C. Experimental Peptic Ulcer Produced by Cinchophen. Methods of Production, the Effect of a Mechanical Irritant, and the Life History of the Ulcer. *Arch. Surg.* **35** 290 (Oct.) 1937. Bollman, J. L., Stalker, L. K., and Mann, F. C. Experimental Peptic Ulcer Produced by Cinchophen, *Arch. Int. Med.* **61** 119 (Jan.) 1938. Stalker, L. K., Boll-

whether the drug is administered by rectum, subcutaneously, intravenously, into an isolated intestinal loop or by mouth. The total gastric secretion was found by these authors to increase twofold or threefold during cinchophen administration, but there was no increase in the acidity. If the prepyloric area was excised, ulcers appeared in the jejunum in 40 per cent of the animals.

Pathologically, such ulcers closely resemble those seen in man and those obtained by the "duodenal drainage" method of Mann and Williamson. Simonds<sup>33</sup> and also Bollman, Stalker and Mann have described the development of the ulcer in two stages. The primary stage lasts a week or ten days, there are acute diffuse gastritis with edema of the mucosa, plasma cell and lymphocytic infiltration, small hemorrhagic erosions and small fistulous channels in the mucosa containing polymorphonuclear leukocytes. The secondary stage consists of return to normal of most of the stomach but, at the same time, progression of one of the early erosions to a deep chronic ulceration in the prepyloric region, with a necrotic, inflamed base and indurated walls. Lesions of this type extend far into the muscularis and, indeed, may perforate or cause massive hemorrhage by erosion of a blood vessel. They heal in a manner entirely similar to that described by Mann<sup>34</sup> for ulcers produced by "duodenal drainage" and by Caylor<sup>35</sup> for ulcers in human beings. A few days after cessation of cinchophen therapy the necrotic material at the base disappears, clean granulation tissue forms, and the ulcer granulates in from the bottom up. Except for a period of acute toxicity, when there is moderate cloudy swelling in the liver and kidneys, no damage to the liver is noted even after prolonged administration of the drug, and no other pathologic changes in other organs are observed.

Diet during the administration of cinchophen appears to have a definite relation to the formation of the ulcers. Thus Stalker and his co-workers<sup>36</sup> found that coarse food hastened the formation of ulcers, while a milk diet delayed them and produced subacute ulcers. If alkalis and a soft diet were given, no ulcers appeared. Likewise, Reid and Ivy<sup>37</sup> found that if 30 Gm. of gastric mucin was given three times a day

man, J. L., and Mann, F. C. Effect of Cinchophen on Gastric Secretion. An Experimental Study, *Arch Surg* **34** 1172 (June) 1937.

33 Simonds, J. P. Mode of Origin of Experimental Gastric Ulcer Produced by Cinchophen, *Arch Path* **26** 44 (July) 1938.

34 Mann, F. C. Production and Healing of Peptic Ulcer. An Experimental Study, *Minnesota Med* **8** 638, 1925.

35 Caylor, H. D. Healing of Ulcer in Man, *Ann Surg* **83** 350, 1926.

36 Stalker, L. K., Bollman, J. L., and Mann, F. C. Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, *Am J Digest Dis & Nutrition* **3** 822, 1937.

37 Reid, P. E., and Ivy, A. C. Gastric Mucin a Prophylactic Against Gastro-Duodenal Ulcers and "Acute" Toxicity Resulting from Cinchophen, *Proc Soc Exper Biol & Med* **34** 142, 1936.

to dogs receiving cinchophen, only 18 per cent had ulcers in eighty days, while 100 per cent of the controls had ulcers in from seven to fifty-nine days

Thus it can be seen that, although the reason for the development of the cinchophen ulcer is not clear, the lesion is pathologically similar to that seen in man, and its response to alkaline diet therapy is likewise parallel

#### METHOD

Two series of dogs were studied. In one group cholecystogastrostomy was performed, with ligation and division of the common duct. After recovery from the operation, administration of cinchophen was begun, and the course was observed. The other group served as controls, and addition of cinchophen to the diet was the only procedure employed. Both groups were fed the same diet, a commercial ground meal preparation, and enjoyed identical living conditions and general care.

The animals were unselected, healthy laboratory dogs which varied in weight from 7 to 23 Kg. Old cinchophen, obtained from Sharp and Dohme, was given in doses of 150 to 200 mg per kilogram of body weight five days a week. In some instances the dogs took the drug in pill form embedded in a small meat ball, in other cases it was necessary to give it in capsules.

The operative technic closely followed that outlined by Walters<sup>38</sup>. With the dog under intravenous pentobarbital sodium anesthesia an incision was made just to the right of the midline, the rectus muscle being retracted laterally. The common duct was identified, doubly ligated above and below and severed. The gallbladder was then mobilized by blunt dissection from its hepatic bed. Oozing was controlled by hot packs. The fundus of the gallbladder was then anastomosed to the anterior wall of the stomach  $2\frac{1}{2}$  to 3 inches (6.2 to 7.6 cm) above the pylorus. The stoma was about 2 cm in length and was closed with three suture lines of fine silk: a mucosa to mucosa Connell suture, a continuous muscularis and serosa suture and a peripheral serosa to serosa suture. One or two stay sutures were placed to hold the omentum around the anastomosis. Hemostasis was easily accomplished except for moderate bleeding from the muscularis of the gallbladder. No intestinal clamps were employed. The wound was closed with silk in most cases, although no. 1 chromic catgut was occasionally used on the peritoneum. A subcuticular skin suture was employed, and the wound was left without dressing. Postoperative care consisted of giving an ample supply of water, no food by mouth for twenty-four hours, milk diet for two days and then a soft solid diet for five days. At the end of the first week most of the dogs seemed completely recovered, and they were then returned to their runways. Administration of cinchophen was sometimes begun as early as the tenth or twelfth postoperative day.

The control series of animals comprised 8 dogs. A summary of the protocols of these dogs is given to show the variations in the response to cinchophen of the normal animal.

#### PROTOCOLS

Dog 1—A dog weighing 51 Kg died five days after administration of cinchophen was begun.

*Gross Observations*—There were marked emaciation, hemorrhagic gastritis and enteritis, with hemorrhage into the intestinal tract.

38 Walters, W. Cholecystogastrostomy. Surg. Gynec. & Obst. 42: 825, 1926.



Fig 1 (dog 2) —Photomicrograph of the margin of a gastric ulcer, showing the overhanging mucosa and the indurated edge  $\times 41$



Fig 2 (dog 2) —Photomicrograph of the margin of an ulceration of the ileum, showing destruction of the mucosa, extension through the muscularis mucosae and marked inflammation  $\times 41$

*Microscopic Observations*—The gastric ulcerations were multiple and small and extended to involve the muscularis mucosae. The mucosa was destroyed in these areas, much brown pigment was present, and the base showed definite leukocytic infiltration. There were small ulcerations of the ileum, extending down to but not involving the muscularis mucosae. The liver cells showed cloudy swelling. The renal tubules showed cloudy swelling and contained hyaline droplets in their lumens.

Dog 2—A lanky dog weighing 9 Kg died on the thirteenth day of administration of cinchophen. Autopsy was performed about ten minutes post mortem.

*Gross Observations*—The dog was emaciated. The stomach showed a small, deep ulcer just above the pylorus, on the lesser curvature. There were many ulcerations throughout the small bowel, with gross hemorrhage into the intestinal tract.

*Microscopic Observations*—The gastric ulcer showed sharp, undermined edges, with induration, the base was composed of necrotic tissue, fibrin, connective tissue and leukocytes. It extended well through the muscularis mucosae. The ulcers in the jejunum and ileum extended through to the muscle wall. Their base consisted of partially necrotic, inflamed granulation tissue. The mucosa was entirely destroyed. Strands of inflammatory leukocytes extended deep into the muscularis along the perivascular lymphatics. Masses of mixed bacteria were seen on the surface of the ulcers. The colonic mucosa showed a diffuse surface inflammation. The vessels were congested, acute leukocytic infiltration was seen, and the superficial third of the mucosa showed necrotic changes. Masses of bacteria were seen clinging to the surface. The renal tubules showed cloudy swelling, and many of the cells contained masses of brown pigment.

Dog 3—A dog weighing 7.4 Kg died rather suddenly on the fourteenth day of cinchophen treatment.

*Gross Observations*—The peritoneal cavity contained gross blood. The stomach contained a deep, punched-out, perforated gastric ulcer 1 cm in diameter in the lesser curvature, just above the pylorus.

*Microscopic Observations*—Section of the ulcer showed the mucosa to end abruptly and the submucosa to be thickened and edematous for some distance on each side. The ulcer extended perpendicularly through the mucosa, its walls were infiltrated, and its base was acutely inflamed. Considerable autolysis was present at the base and involved the peritoneal surface as well. The peritoneum was covered with an acute fibrinopurulent exudate. The rest of the gastrointestinal tract was autolyzed but otherwise normal except for diffuse peritonitis. The renal tubules were degenerated and contained granular and hyaline casts. Many glomeruli contained granular exudate within the capsular space. Small infarctions with glomerular degeneration and lymphocytic infiltration were seen.

Dog 4—A collie weighing 10.5 Kg died on the seventeenth day of administration of cinchophen. Autopsy was not performed for several hours after death.

*Gross Observations*—The peritoneal cavity contained gross blood. Autolysis was marked throughout the gastrointestinal tract; no definite gastric ulcers could be seen.

*Microscopic Observations*—Autolysis was pronounced. However, a definite small ulcer was seen in the gastric mucosa associated with diffuse subacute

gastritis A small area of subacute inflammation of the submucosa was seen in the colon

Dog 5—A dog weighing 7 Kg died after eight days of cinchophen treatment.

*Gross Observations*—The dog was emaciated Gross blood was observed in the intestinal tract There were acute gastritis and enteritis

*Microscopic Observations*—There was diffuse acute superficial enteritis, with marked vascular congestion, necrosis and leukocytic infiltration The gastric mucosa seemed to be within normal limits There was congestion of the liver, lung and kidneys

Dog 6—A dog weighing 8 Kg became acutely ill during the first week of administration of cinchophen It seemed to recover, however, but its appetite



Fig 3 (dog 6)—Photograph of the unfixed specimen, the stomach and a portion of the duodenum, showing a large perforated ulcer in the prepyloric area

remained poor, it slowly lost weight, and it finally died, fifty-one days after starting the drug

*Gross Observations*—The dog was very emaciated A large, deep ulcer on the lesser curvature, just above the pylorus, was seen to have eroded through the gastric wall The liver, pancreas and gastrohepatic ligament were bound together in a mass of adhesions at the site of perforation

*Microscopic Observations*—The gastrointestinal tract was normal except for chronic indurated perforated gastric ulcer There was acute local peritonitis The spleen was loaded with phagocytes containing golden-brown pigment The liver and kidneys were normal

Dog 7—A dog weighing 8.5 Kg died on the thirty-second day of administration of cinchophen Autopsy was unavoidably delayed for one day



*Gross Observations*—There were marked emaciation and acute diffuse peritonitis. A large perforated gastric ulcer on the lesser curvature, just above the pylorus, was present. Because of the state of decomposition no sections were made.

Dog 8—A German shepherd dog weighing 22 Kg was given cinchophen in doses of 150 mg per kilogram of body weight for thirty days. The dog showed no toxic symptoms, remained lively and even gained weight. The dose was then increased to 200 mg per kilogram for thirty days. There was no observable effect. The dog was playful, ate well and remained fat. Because the animal was desired for other purposes it was not killed for autopsy, but it was considered that this animal had failed to react to cinchophen with either the acute toxic response or the chronic ulcerative one.



Fig 4 (dog 9)—Photograph of the unfixed specimen, the stomach, gallbladder and duodenum, showing a punched-out ulcer just above the pylorus. The probe indicates the site of the cholecystogastrostomy stoma.

The surgically treated series comprised 5 animals. A summary of their protocols follows.

Dog 9—A dog weighing 13 Kg recovered without incident from the operation. Two weeks after operation administration of cinchophen was begun. The dog seemed well until about the fifteenth day when it began to act ill and to lose weight. It went progressively downhill and died on the thirty-eighth day of administration of cinchophen.

*Gross Observations*—The animal was emaciated. The anastomosis was well healed and patent. The common duct was ligated. There was a 2 cm ulcer on the lesser curvature of the stomach just above the pylorus.

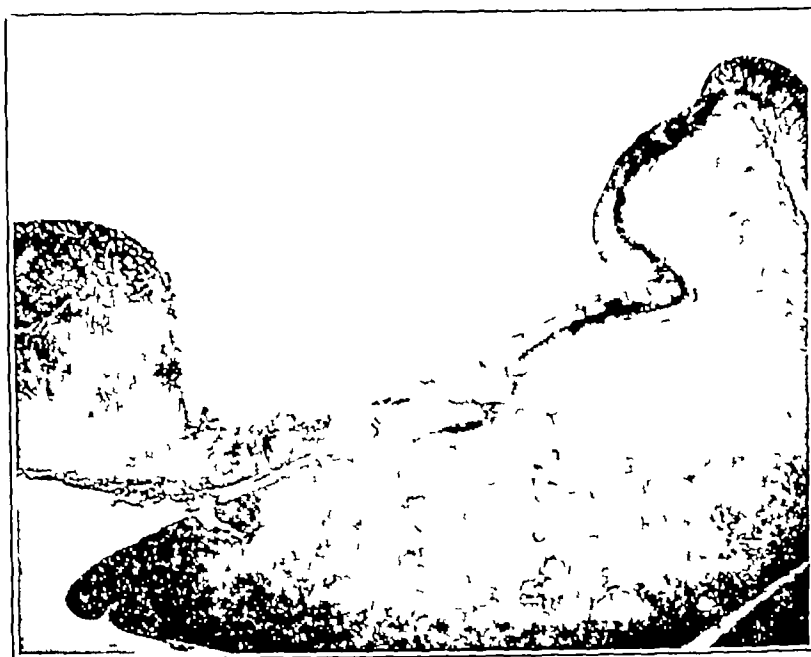


Fig 5 (dog 9) —Photograph of a cross section of the ulcer pictured in figure 4, showing perforation through the wall of the stomach to the liver  $\times 5$



Fig 6 (dog 9) —Photomicrograph of the edge of an ulcer in the ileum, showing destruction of the mucosa and an acute inflammation of the submucosa  $\times 41$

*Microscopic Observations*—Ulcer The ulcer extended entirely through the wall of the stomach, its base being formed by the adherent liver Anastomosis This was firmly healed by fibrosis There was moderate chronic inflammation of the gallbladder Small Bowel There were areas of chronic ulceration extending into the submucosa Kidneys There were degeneration, edema precipitate in the capsular spaces and casts Liver This organ was normal

Dog 10—A German shepherd dog weighing 23 Kg had a rapid, uneventful recovery from operation Administration of cinchophen was begun on the ninth postoperative day The dog was given 5 Gm a day five days a week for sixty days without showing any toxic effect It was then given 6 Gm doses in capsules It began to appear ill, lost weight and died on the one hundred and twenty-first day after administration of cinchophen was started

*Gross Observations*—The stomach contained no ulcers, but scattered throughout the jejunum and ileum were small necrotic ulcerations The stoma was patent and the common duct ligated

*Microscopic Observations*—The stomach was normal except for much submucosal edema, and the anastomosis was well healed The gallbladder was thickened with chronic inflammation The small bowel showed areas of ulceration where the mucosa was destroyed the muscularis mucosae lost and the submucosa thickened and inflamed Some of the liver cells showed degenerative changes The kidneys were normal

Dog 11—A dog weighing 5 Kg recovered rapidly from the operation. Administration of cinchophen was begun on the thirteenth postoperative day The dog soon appeared ill, lost weight and passed tarry stools, it died on the thirteenth day of administration of cinchophen

*Gross Observations*—There was emaciation The stomach appeared normal and the stoma patent, the common duct had been severed The small bowel contained multiple deep red erosions and ulcerations, and there was gross blood in the intestinal contents

*Microscopic Observations*—The stomach, liver and kidneys were normal The stoma was well healed The gallbladder showed subacute inflammation The small bowel revealed multiple hemorrhagic erosions Free hemorrhage occurred into the muscularis, into the submucosa and especially into the base of the mucosa dissecting the glands off the basement membrane Around the areas of hemorrhage there was an acute inflammatory reaction Macrophages containing brown pigment could be seen in these areas The large bowel contained ulcerations a chronic inflammatory reaction of the submucosa forming the base The spleen was crowded with macrophages filled with brown pigment

Dog 12—A dog weighing 10 Kg made an uneventful recovery from operation Administration of cinchophen was begun three weeks after operation For two months it was administered in meat balls there was not much evidence of toxicity The dog then began to refuse the drug and so it was administered in capsules The animal soon began to appear somewhat thinner and less responsive but not acutely ill Surgical exploration was done on the one hundred and eighteenth day of administration of cinchophen No gastric lesion was found On the sixth postoperative day the dog was eviscerated in a fight and died

*Gross Observations*—There was evisceration Three major hepatic ducts fused to form the common duct, and the cystic duct came off one of the hepatic ducts This hepatic duct had been ligated and severed Part of the bile, therefore had

entered the intestinal tract via the common duct and part via the cholecystogastrostomy opening. A 6 mm ulcer was found just distal to the pylorus in the posterior duodenal wall.

*Microscopic Observations*—The stomach contained small areas of subacute inflammation deep in the mucosa, involving the muscularis mucosae. The anastomosis was firmly knit and the mucosal surface entirely covered. The ulcer had a chronically inflamed base extending through the muscularis, with considerable fibrosis of the surrounding tissue. Recent acute inflammation, extending in under the edges and involving the adjacent muscularis, was seen. The liver showed subacute inflammation in the periportal areas, suggesting early cholangitis. The kidneys were normal.

Dog 13—A dog weighing 7 Kg seemed to lose its appetite after operation and loss of weight. However, it soon began to eat better, and it seemed well when administration of cinchophen was begun, four weeks after operation. It rapidly became sick, vomited, passed tarry stools and refused food. It died on the ninth day of treatment.

*Gross Observations*—The dog was thin. A large, deep ulcer was located on the lesser curvature, just above the pylorus.

*Microscopic Observations*—The ulcer showed an inflamed base extending all the way through the muscularis, the pancreas and the liver were adherent at this point. The edges were undermined and inflamed. The anastomosis was well healed, there was cholecystitis. The stomach was moderately congested, one small area of acute inflammation of the mucosa and submucosa was seen. Elsewhere it was normal. The liver showed acute cholangitis, but the parenchyma was not involved. The renal tubules showed slight cloudy swelling.

## RESULTS

There was little observable difference in the reaction of the two series of animals to administration of cinchophen. All the animals in the group operated on and all but 1 of the control group showed gastrointestinal lesions which led to a fatal termination. Both groups likewise responded with a similar clinical reaction and a similar pathologic picture. From about the third to the eighth day there was a period of apparent acute toxemia—the animals lost their vigor, refused to eat, suffered nausea and vomiting and lost weight. Some of the animals died in this stage, and acute gastritis and enteritis were observed, together with cloudy swelling in the liver and kidneys. The lesions were diffuse, usually superficial, hemorrhagic and acutely inflamed. If the animal survived this period it seemed to become much less ill, energy and responsiveness returned, and it began to eat. Soon, however, it started to become thin. It tended to sit in a characteristic manner, the forefeet very close to the hindfeet and the abdomen drawn in as if the animal were suffering abdominal pain. Death for these animals was often rapid, following a perforation, or was preceded by a day or two of tarry stools indicating gross intestinal hemorrhage. Autopsy revealed a single

deep gastric or duodenal ulcer, multiple deep jejunal and ileal ulcers or, as in 1 animal, both types of lesions. The liver and kidneys tended to be normal. The accompanying table demonstrates this similarity of response of the two groups of animals.

#### COMMENT

The pathologic progress in both series of animals was entirely similar to that described by Bollman and his associates and by Simonds. Acute hemorrhagic and edematous gastritis with scattered areas of acute inflammation first appeared. These lesions then regressed, the mucosa tended to become normal except for one ulcer, which increased in size, the edges became undermined, and the ulcer extended deep into the muscularis. The lesion was almost invariably situated just above the pylorus, on the lesser curvature.

Several of the animals had similar ulcerations throughout the small bowel, a condition not emphasized in previous communications. In the acute phase these consisted of multiple scattered areas of hemorrhagic

#### *Pathologic Observations*

	Acute Gastritis and Enteritis	Chronic Peptic Ulcer	Ulcerative Enteritis	No Lesions
Control dogs	2	4	2	1
Surgically treated dogs	1	3	1	0

erosion and acute inflammation, with strands and masses of polymorphonuclear cells appearing in the mucosa. In the later stage the ulcerations became less numerous but much larger and deeper, being in some instances 2 or 3 cm. in diameter and extending halfway around the lumen of the intestine. The mucosa ended abruptly, and the adjacent submucosa was thickened and chronically inflamed. The base of the lesion was formed by thickened submucosa. The muscularis mucosae was destroyed, and the surface consisted of acute inflammatory tissue and necrotic debris. Rarely did these lesions extend into the muscularis itself, and, while hemorrhage from them was commonly observed, they were never seen to have perforated. The edges of such lesions are to be seen in figures 2 and 6. Whatever is the mode of action of cinchophen in causing gastrointestinal ulcerations, it seems apparent that it exerts its toxic effect throughout the length of the bowel.

My material also confirms the finding of others that there is no chronic or severe damage to the liver despite the massive and prolonged administration of cinchophen. Some cloudy swelling is noted in the acute toxic phase, but this tends to clear up. The only animal showing definite change in the liver was the dog who survived five months after

operation This was subacute cholangitis, a lesion which has been found by many workers to appear almost invariably in dogs after cholecystogastrostomy This subject has been reviewed by Gentile<sup>39</sup>

The presence of a brownish pigment noted microscopically in several of the animals is of interest It was seen in 1 case in the ulcerated areas in the stomach, in 2 in macrophages in the spleen and in 1 in the kidneys It did not take an iron stain The relation of this to the mode of action of cinchophen is not clear, but that there is a relation seems highly probable

#### SUMMARY AND CONCLUSIONS

Two series of animals were fed old cinchophen five days a week On one group, of 5 dogs, previous cholecystogastrostomy with ligation of the common duct was performed, the other group, of 8 dogs, served as controls

No significant difference in the incidence of gastrointestinal ulcerations was noted in the two groups All the animals of the surgically treated group and all but 1 of the control group died of intestinal lesions

The presence of bile in the stomach is not adequate to protect that organ from the cinchophen-induced ulcer

A hitherto unemphasized ulcerative enteritis occurring in a good percentage of both groups is described

Cinchophen appears to be toxic to the mucosa of the entire intestinal tract

Dr W C Black furnished helpful criticisms and guidance throughout the work described

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<sup>39</sup> Gentile, A Cholecystogastrostomy and Hepatitis, Arch Surg 30 449 (March) 1935

# METABOLISM OF VITAMIN K AND ROLE OF THE LIVER IN PRODUCTION OF PRO-THROMBIN IN ANIMALS

JERE W LORD JR, MD

WILLIAM DEW ANDRUS, MD

AND

ROBERT A MOORE, MD

NEW YORK

The hemorrhagic tendency associated with obstructive jaundice, with prolonged biliary fistula and with certain types of hepatic damage has been a well recognized clinical entity for many years. However elucidation of the underlying cause of the bleeding has been accomplished only recently. There have been many experimental studies of the various components of the blood which play a role in the process of coagulation, and until lately the cause of the clotting defect had not been found. Moss<sup>1</sup> in 1933 demonstrated that the concentration of plasma fibrinogen is normal in dogs with obstructive jaundice. Carr and Foote<sup>2</sup> in 1934 confirmed the results of Moss and showed that massive parenchymatous hemorrhage occurred in dogs with obstructive jaundice if life was prolonged to fifteen weeks.

In 1935 and 1936 Hawkins and Whipple<sup>3</sup> and Hawkins and Brinkhous<sup>4</sup> demonstrated the hemorrhagic tendency in dogs with biliary fistulas and showed that the bleeding was due to a deficiency of plasma prothrombin. The relation of vitamin K and the level of plasma pro-

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From the Department of Surgery and Department of Pathology of the New York Hospital and Cornell University Medical College.

1 Moss, W. Experimental Obstructive Jaundice. Its Effect on Fibrinogen and Coagulation of the Blood, *Arch Surg* **26** 1-19 (Jan) 1933.

2 Carr, J. L., and Foote, F. S. Progressive Obstructive Jaundice. Changes in Certain Elements of Blood and Their Relation to Coagulation, *Arch Surg* **29** 277-296 (Aug) 1934.

3 Hawkins, W. B., and Whipple, G. H. Bile Fistulas and Related Abnormalities. Bleeding, Osteoporosis, Cholelithiasis and Duodenal Ulcers. *J. Exper Med* **62** 599-620 (Oct) 1935.

4 Hawkins, W. B., and Brinkhous, K. M. Prothrombin Deficiency the Cause of Bleeding in Bile Fistula Dogs, *J. Exper Med* **63** 795-801 (June) 1936.

thrombin in dogs with biliary fistulas was determined by Smith, Warner, Brinkhous and Seegers<sup>5</sup> in 1938

In 1937 Smith, Warner and Brinkhous<sup>6</sup> showed the intimate relation between plasma prothrombin and hepatic function by damaging the livers of dogs with chloroform. In their experiments the level of plasma prothrombin fell rapidly to 5 to 10 per cent of normal within twenty-four hours in cases of acute poisoning, and six to seven days elapsed before the return to normal was complete. Warner<sup>7</sup> performed partial hepatectomy in rats and was able to bring about a fall in the plasma prothrombin to 30 to 40 per cent of normal.

The experimental work on which the present paper is based is the study of the role of vitamin K and the liver in the formation of plasma prothrombin in the dog.

#### METHODS

Normal mongrel dogs weighing between 25 and 40 pounds (11.3 and 18.1 Kg) were used, and obstructive jaundice was produced in certain of them by division of the common bile duct between ligatures. In some of these animals a cholecystectomy was also performed. Biliary fistulas were established in other dogs by the technic of Kapsinow, Engle and Harvey<sup>8</sup> by means of cholecystonephrostomy after ligation of the common duct. Total hepatectomy was performed by the methods of Mann<sup>9</sup> and of Markowitz, Yater and Burrows<sup>10</sup>. The technic of Warner, Brinkhous and Smith<sup>11</sup> was used in all determinations of the value for plasma prothrombin, and the vitamin K content of the livers was assayed by the curative method.

The diet of all the animals was carefully regulated, since Bollman and Mann<sup>12</sup> have demonstrated the importance of diet in any experimental study of the func-

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5 Smith, H. P., Warner, E. D., Brinkhous, K. M., and Seegers, W. H. Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs. Effect of Feeding Bile and Vitamin K, *J. Exper. Med.* **67** 911-920 (June) 1938.

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11 Warner, E. D., Brinkhous, K. M., and Smith, H. P. A Quantitative Study on Blood Clotting. Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114** 667-675 (Feb) 1936.

12 Bollman, J. L., and Mann, F. C. The Physiology of the Impaired Liver, *Ergebn. d. Physiol.* **38** 445-492, 1936.



tion of the liver. A high carbohydrate, low fat, meat-free diet not only is of value in maintaining the health of dogs with hepatic damage but is effective in prolonging the life of animals with obstructive jaundice. The composition of the diet employed in all experiments was as follows:

<i>Diet D-3</i>		
Food		Amount
Milk		500 cc
Bread		4 slices
Karo		100 cc
Tomato juice		30 cc
Cod liver oil		4 cc
Brewers' yeast		2 Gm
Iron and ammonium citrates (50% solution)		4 cc to each quart of tomato juice

This diet contains 32 Gm of protein, 5 Gm of fat and 184 Gm of carbohydrate and has an approximate total caloric value of 909 calories. To illustrate the effectiveness of this diet in prolonging the lives of dogs with obstructive jaundice, two groups of animals are compared, one of which was fed a stock kennel food called diet D-1 while the other was fed the special diet D-3.

	Number of Dogs	Average Num- ber of Days
Diet D-1	4	47
Diet D-3	5	75

#### OBSTRUCTIVE JAUNDICE

In 1934, Carr and Foote<sup>2</sup> produced in dogs the hemorrhagic tendency associated with obstructive jaundice. Their animals lived approximately fifteen weeks, and death was due to massive hemorrhage in 3 experiments and to hepatic insufficiency associated with cirrhosis in 2 others. They noted in the later stages of the experiments that, although the clotting time did not become prolonged, the clot was defective. It was bulky and fragile and failed to retract satisfactorily. The level of plasma fibrinogen showed no change during the experiment, thereby confirming the work of Moss,<sup>1</sup> who, in 1933, had failed to observe any change in this substance in dogs with biliary obstruction.

That the hemorrhagic tendency associated with obstructive jaundice in dogs is the result of a plasma prothrombin deficiency is evident in chart 1. After ligation and division of the common bile duct the plasma prothrombin fell progressively to 15 per cent of normal in one hundred and five days. The death of the animal on the one hundred and eighteenth day was due to perforation of a duodenal ulcer and peritonitis.

In a group of 8 dogs in which obstructive jaundice was produced and which lived sixty-five days or more after operation, 3 exhibited parenchymatous hemorrhage at autopsy. For 2 of these 3 dogs the value for plasma prothrombin was below 20 per cent of normal while for the third it was 30 per cent of normal.

All 8 animals showed reduced levels of plasma prothrombin, and at autopsy the livers were observed to be small, firm, dark green and mottled. On section the liver revealed white strands of fibrous tissue. Microscopically the picture was one of obstructive biliary cirrhosis, with a moderate amount of connective tissue bridging the portal spaces and infiltration with lymphocytic and a few mononuclear cells. Centrally, the biliary canaliculi contained plugs of inspissated bile. A characteristic observation in all but 2 animals was one or more duodenal ulcers, and in 2 instances perforation of the ulcer was directly responsible for the animal's death. In no dog was any bile found in the intestinal tract.

It seems evident from these experiments on the dog that the fall in plasma prothrombin associated with obstructive jaundice may be due to one or two factors or to their combination. In the first place, owing to ligation and division of the common ducts, bile cannot reach the intestinal tract, and presumably absorption of fat-soluble vitamins, such as vitamin K, is defective. Prothrombin formation is thereby interfered

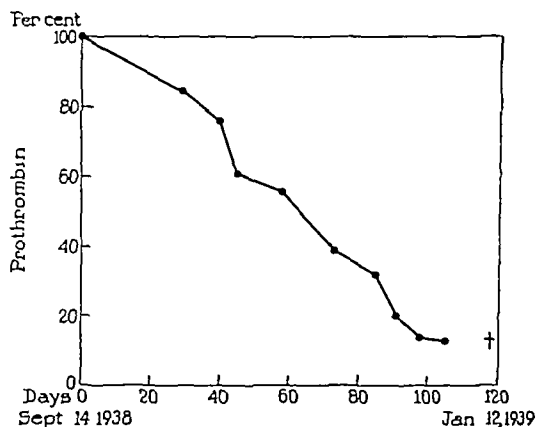


Chart 1—Effect of ligation of the common bile duct on the level of plasma prothrombin

with as the available stores of vitamin K are exhausted. Secondly, obstructive jaundice produces a conspicuous change in the liver, the later stage of which is represented by obstructive biliary cirrhosis, and hepatic functions—among them the production of prothrombin—suffer concomitantly with the morphologic changes in the liver.

#### BILIARY FISTULA

In order to eliminate the factor of obstructive cirrhosis, dogs were subjected to cholecystonephrostomy and division and ligation of the common bile duct by the method described by Kapsinow, Engle and Harvey. In 1935, Hawkins and Whipple<sup>3</sup> reported a variety of abnormalities which followed the establishment of biliary fistulas in dogs by this method, and among the changes noted purpura and spontaneous bleeding were conspicuous. Three to four months elapsed before hemorrhages were observed, and these investigators stated the belief that a

deficiency in plasma prothrombin was the underlying cause for the hemorrhage. In the next year Hawkins and Brinkhous<sup>4</sup> demonstrated the deficiency in prothrombin as the cause of the hemorrhagic tendency associated with biliary fistulas of prolonged duration and found that the feeding of whole bile both prevented and cured the condition.

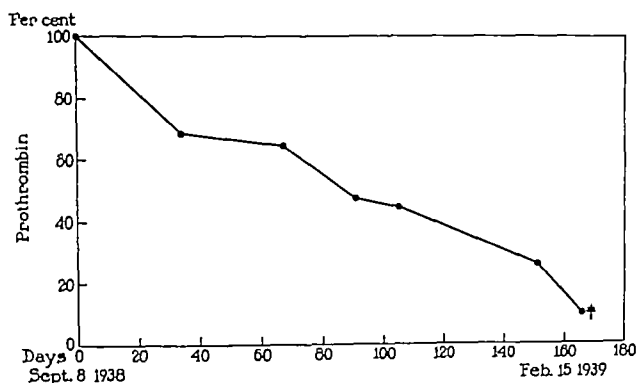


Chart 2—Effect of an internal biliary fistula on the level of plasma prothrombin

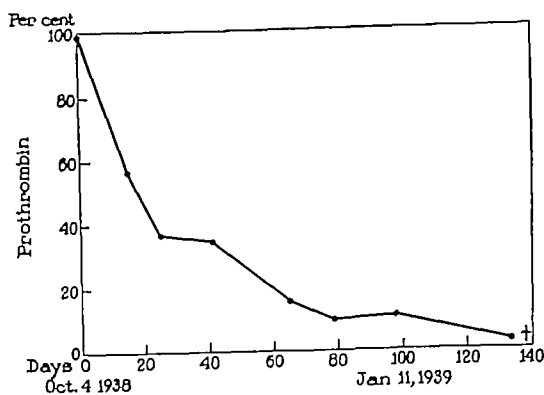


Chart 3—Effect of feeding bile salts, 1 Gm four times a day, to a dog with an internal biliary fistula

Smith, Warner, Brinkhous and Seegers,<sup>5</sup> extending this work, observed that feeding bile salts alone was only partially effective in raising the plasma prothrombin. They found that whole bile was more effective than bile salts in elevating the level of plasma prothrombin but that administration of concentrated vitamin K in the presence of bile or bile salts brought about a rapid increase in the plasma prothrombin. They observed that viosterol was without effect.

An example of the characteristic fall in plasma prothrombin following the exclusion of bile from the intestinal tract but without hepatic damage can be seen

in chart 2 This animal was killed on the one hundred and sixty-fifth post-operative day while in a state of excellent health That bile salts alone are not adequate to maintain the prothrombin level of the blood in the absence of excess vitamin K in the diet is demonstrated in chart 3 The animal represented had a biliary fistula for one hundred and thirty-five days and died as a result of a massive gastrointestinal hemorrhage with a plasma prothrombin level of only 5 per cent of normal Autopsy demonstrated that the bleeding was parenchymatous

Administration of bile salts with adequate intake of vitamin K, however, brings about a prompt rise of the level of plasma prothrombin (chart 4) The animal represented had a low level of plasma prothrombin as a result of a long-standing biliary fistula, and when 14,000 units of vitamin K (klotogen) and 14 Gm of bile salts (bilron) were fed over a period of twelve days, the level of plasma prothrombin rose from 10 per cent to 70 per cent of normal It is worthy of note that when the vitamin K therapy was discontinued there was a prompt fall in plasma prothrombin to a level of 20 per cent in eight days, indicating that storage of the vitamin in the liver had apparently not taken place

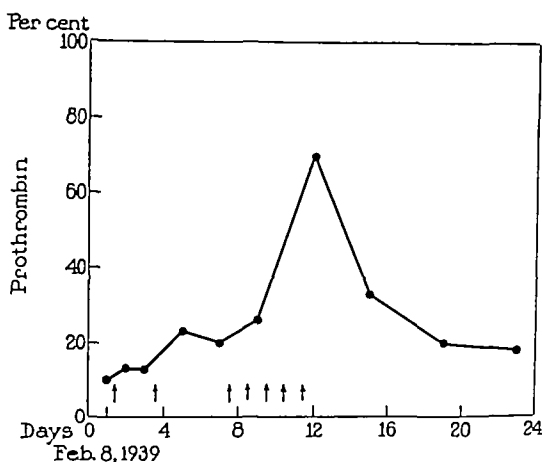


Chart 4—Effect of feeding vitamin K (2,000 units) and bile salts (2 Gm) to a deficient dog with an internal biliary fistula

In order to investigate the relation between the level of plasma prothrombin and the amount of vitamin K in the liver, the vitamin K content of the livers of the aforementioned 14 dogs was assayed In all, 7 dogs were subjected to ligation and division of the common bile duct, 5 dogs had biliary fistulas, and 2 animals (not operated on) were kept on the same diet as the operative groups for a similar length of time, approximately one hundred days The liver of each animal was removed at autopsy after the dog had either been killed or died, and was dried by the cryochem process The dried liver was then assayed for the curative value in vitamin K-deficient chicks Chart 5 shows a spot graph of the results in which the terminal value for plasma prothrombin of the dog is plotted against the Howell prothrombin time of the treated chicks

The normal liver evidently contains sufficient vitamin K so that the prothrombin time of the chicks to which it is fed is from six to ten minutes by the curative method of assay Livers devoid of vitamin K are indicated by the chick's prothrombin time of thirty minutes It is clear from the chart that there is a linear relation between the level of the plasma prothrombin and the vitamin K content of the liver This is evidence that the value for plasma prothrombin falls

concomitantly with the depletion of the store of vitamin K in the liver, and that the fall is not delayed until the store is exhausted

In order to observe the effect of instillation of vitamin K and bile salts directly into the duodenum at laparotomy, a dog with a biliary fistula which had a plasma prothrombin concentration of 18 per cent was operated on, and 10,000 units of

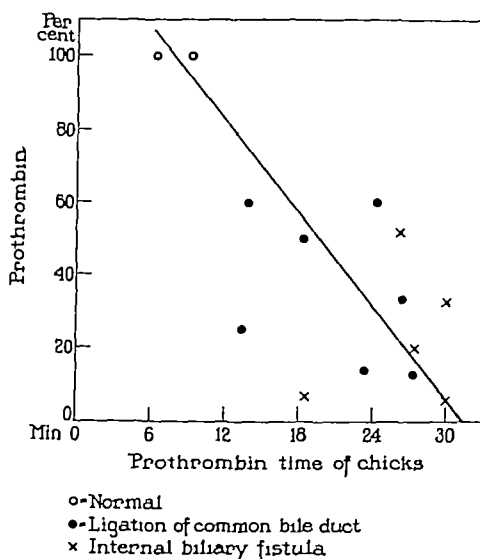


Chart 5—Vitamin K content of the liver in relation to plasma prothrombin

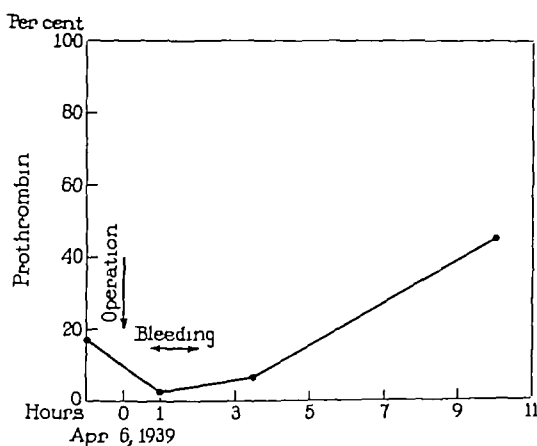


Chart 6—Effect of instillation into the duodenum at laparotomy of 10,000 units of vitamin K and 2 Gm of bile salts in a dog with an internal biliary fistula

vitamin K (klotogen) and 2 Gm of bile salts (bilron) were instilled directly into the duodenum. The level of plasma prothrombin fell immediately postoperatively, and associated with this there was hemorrhage from the wound. Within ten hours of the operation the level of plasma prothrombin had risen to 45 per cent of normal (chart 6). Twenty-one hours after the instillation of vitamin K the value was 65 per cent of normal. Three days later it had again fallen to less than 5 per cent of normal.

## ROLE OF LIVER IN SYNTHESIS OF PROTHROMBIN

Smith, Warner and Brinkhous,<sup>6</sup> using chloroform as the hepatotoxin, observed a precipitous fall in plasma prothrombin to less than 10 per cent of normal within twenty-four hours of the chloroform anesthesia, and the return to normal was not complete until six days had elapsed. With the foregoing evidence in mind, we have studied the plasma prothrombin after a variety of injuries to the liver (1) mechanical trauma, (2) partial hepatectomy and (3) total hepatectomy.

The effect of mechanical trauma to the liver on the plasma prothrombin was investigated by one of us (J W L<sup>13</sup>), and it was found that after gentle massage of the liver for twenty-five minutes a precipitous fall occurred in the level of plasma prothrombin to 75 per cent of normal and that the return to normal was not complete until sometime between the fourth and the seventh postoperative day (chart 7). Simple laparotomy and operations of the magnitude of a gastroenterostomy were without effect on the plasma prothrombin.

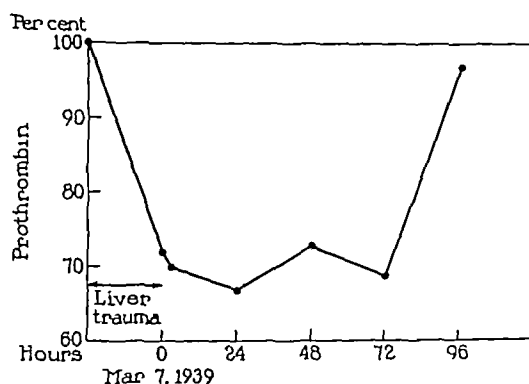


Chart 7—Effect of mechanical trauma to the liver on the level of plasma prothrombin

Partial hepatectomy in which approximately 25 per cent of the liver was removed in 1 dog was followed by a progressive fall in the level of plasma prothrombin to 60 per cent of normal within forty-eight hours and a return to normal after seven days. A second animal showed a similar fall in the level of plasma prothrombin following partial hepatectomy but died of bronchopneumonia on the third postoperative day.

Andrus, Lord and Moore<sup>14</sup> and Warren and Rhoads<sup>15</sup> independently performed total hepatectomy in dogs and found that the plasma prothrombin fell progressively to low levels. The former investigators

13 Lord, J W, Jr. The Effect of Trauma to the Liver on the Plasma Prothrombin. An Experimental Study, *Surgery* 6 896-898 (Dec) 1939

14 Andrus, W DeW, Lord, J W, Jr, and Moore, R A. The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* 6 899-900 (Dec) 1939

15 Warren, R, and Rhoads, J E. The Hepatic Origin of the Plasma-Prothrombin Observations After Total Hepatectomy in the Dog. *Am J M Sc* 198 193-197 (Aug) 1939

found that the concentration fell to less than 20 per cent of normal in ten hours and to 5 per cent of normal in 2 dogs that lived longer than ten hours (chart 8) and that instillation of 10,000 units of vitamin K and 2 Gm of bile salts into the duodenum at the end of the operation failed to alter the typical curve observed in the hepatectomized animals without such instillation

It is evident that, regardless of the mode of injury to the liver, such injury is reflected in a prompt fall in the concentration of plasma prothrombin

#### COMMENT

In many respects there is some similarity between the underlying mechanism responsible for the bleeding tendency due to lowered concentrations of plasma prothrombin and that producing anemia of the

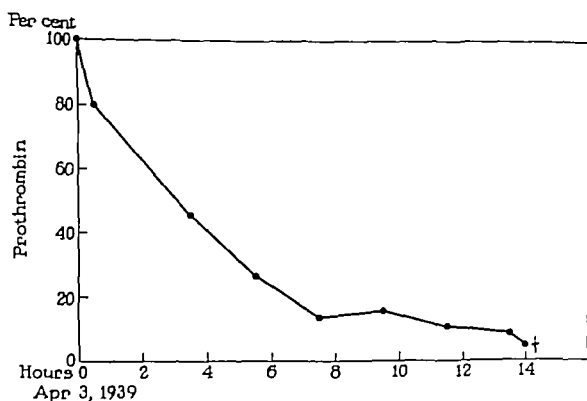


Chart 8—Effect of total hepatectomy on the level of plasma prothrombin

addisonian type In the latter the extrinsic factor in the diet is comparable to vitamin K itself, while the intrinsic gastric factor may be compared to the bile salts needed for absorption of vitamin K In the young chicken, lowered levels of plasma prothrombin have been occasioned by diets deficient in vitamin K In the dog, absence of bile salts in the intestinal tract is responsible for failure of absorption of vitamin K Whether there is an actual chemical reaction between this vitamin and bile salts or whether the bile salts act simply as a carrier of the vitamin K across the intestinal epithelium is as yet unsettled That the latter view is probably correct is substantiated by the prompt and significant rise of 30 per cent in the plasma prothrombin within forty-eight hours in dogs given intramuscular injections of crystalline vitamin K principle, 2-methyl-1, 4-naphthoquinone in oil<sup>16</sup> Doses as small as 1 mg

<sup>16</sup> Andrus, W DeW and Lord J W Jr The Correction of Prothrombin Deficiency by Means of 2-Methyl-1 4-Naphthoquinone Injected Intramuscularly J A M A **114** 1336 1337 (April 6) 1940

are effective. The lack of the intrinsic factor in the stomach in the presence of pernicious anemia and the defective absorption of the combined factor in the presence of sprue both act to deprive the liver of the anti-anemic factor. Likewise, the absence of bile salts in the intestine in the presence of obstructive jaundice or biliary fistula results in failure of absorption of vitamin K and therefore deprives the liver of that necessary element in the formation of plasma prothrombin.

That the liver forms plasma prothrombin is established beyond a reasonable doubt by the experimental evidence concerning the dog just mentioned. Total or partial removal of the liver and mechanical or chemical trauma to the liver are reflected by prompt changes in the concentration of plasma prothrombin. In the dog with total extirpation of the liver the plasma prothrombin falls to extremely low levels (less than 10 per cent of normal), and the hemorrhagic diathesis becomes manifest in as short a period as fourteen hours after the operation. Similarly, in the presence of chronic hepatic insufficiency as seen in cases of cirrhosis of the liver, in human beings, a macrocytic anemia is a prominent feature of that disease. As the liver stores the antianemic principle, it likewise stores vitamin K in dogs. This storage is evidenced by the protective action of the dried livers of dogs when assayed in vitamin K-deficient chicks.

In resume, into the final formation of plasma prothrombin there enter an extrinsic factor, vitamin K, an intrinsic factor, bile salts, an absorptive mechanism, the intestinal epithelium, and the liver, which, in the case of plasma prothrombin, not only stores vitamin K but elaborates the plasma prothrombin.

The fate of plasma prothrombin after its formation in the liver and release into the circulating blood has been the subject of some recent experimental work.<sup>17</sup> Certain studies point to the lungs as the site of disappearance of plasma prothrombin. Samples of circulating blood taken simultaneously from the arterial and the venous supply of various organs in the dog revealed no significant variation in the level of plasma prothrombin with the one exception of blood circulating to and from the lungs. In 17 of 20 experiments (85 per cent) plasma prothrombin in the samples of blood taken from the left ventricle averaged 10.6 per cent less than in samples from the right ventricle.

A possible explanation of this role of the lung in the loss of plasma prothrombin is thought to be the production of blood platelets in this organ, as demonstrated by Howell and Donahue.<sup>18</sup> Platelets, as they

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17 Andrus, W. DeW., Lord, J. W., Jr., and Kauer, J. T. Studies on the Fate of Plasma Prothrombin, *Science* **91** 48-50 (Jan 12) 1940.

18 Howell, W. H. and Donahue, D. D. The Production of Blood Platelets in the Lungs, *J. Exper. Med.* **65** 177-203 (Feb.) 1937.



undergo disintegration, initiate the first stage of the clotting process by releasing thromboplastin, which, in the presence of calcium, changes prothrombin to thrombin

#### SUMMARY AND CONCLUSIONS

A brief historical resume of some of the experimental evidence concerning the relation between the hemorrhagic diathesis, plasma prothrombin and vitamin K is presented

The protective effect on the liver of a carefully selected diet is demonstrated

Bile must reach the intestinal tract for the proper absorption of the fat-soluble vitamin K. The essential substance in bile is the bile salts

In dogs with obstructive jaundice or biliary fistula, bile salts alone when fed by mouth in the absence of added vitamin K do not suffice to prevent a fall in the level of plasma prothrombin

Vitamin K after absorption is stored in the liver. Partial loss of the stores of vitamin K in the liver is reflected in a linear manner by a fall in the level of plasma prothrombin

The liver is the site of formation of plasma prothrombin. A healthy, normally functioning liver is required for the maintenance of a normal level of plasma prothrombin

A comparison has been made between the factors whose derangement results in pernicious anemia and the vitamin K-plasma prothrombin relation. That these two entities are decidedly similar physiologically and anatomically is noted

Prothrombin is continuously disappearing from the circulating blood, and experiments point to the lung as the site of this loss

When plasma prothrombin falls to low levels because of inadequate absorption, hepatic damage or both, the hemorrhagic tendency becomes manifest. The critical level of the plasma prothrombin is approximately 20 per cent of normal by the method used in these studies

# CLINICAL INVESTIGATIONS OF SOME FACTORS CAUSING PROTHROMBIN DEFICIENCIES

SIGNIFICANCE OF THE LIVER IN THEIR PRODUCTION AND CORRECTION

WILLIAM DeW ANDRUS, M D

AND

JERE W LORD JR, M D

NEW YORK

The hemorrhagic tendency sometimes seen in patients with obstructive jaundice has been the subject of a great deal of clinical and experimental investigation since Smith<sup>1</sup> remarked on it nearly fifty years ago. This has now culminated in discovery of the underlying deficiency and of measures by which it can promptly be corrected in most cases. In the process of the investigations many bypaths have also been explored, and while in them the ultimate cause was not found, among the accumulated data facts were encountered which contributed to the final solution of the problem. The spectacular developments of the past few years are due in part at least to such facts and to theories developed over many years as one after another of the recognized clotting elements of the blood was considered as possibly involved and then dismissed.

A deficiency of calcium was long held to be of importance,<sup>2</sup> and as finer methods became available for studying the various fractions of this element in the blood, these too were studied,<sup>3</sup> but without consistent results. Changes in the fibrinogen content of the blood were also considered, but such alterations as were demonstrable in cases of obstructive jaundice were not consistent and tended to be on the side of increase rather than of decrease in this component.<sup>4</sup>

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This study was carried out under a grant from the John and Mary R Markle Foundation.

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1 Smith, G. Abdominal Surgery, Philadelphia, P. Blakiston's Son & Co., 1891, p. 610.

2 King, J. H., and Stewart, H. A. The Effect of the Injection of Bile on the Circulation, *J. Exper. Med.* **11** 673, 1909. Walters, W. Pre-Operative Preparation of Patients with Obstructive Jaundice, *Surg., Gynec. & Obst.* **33** 651, 1921. Lee, R. I., and Vincent, B. The Relation of Calcium to the Delayed Coagulation of Blood in Obstructive Jaundice, *Arch. Int. Med.* **16** 59 (July) 1915.

3 Gunther, L., and Greenberg, D. M. Diffusible Calcium and Protein of Blood Serum in Jaundice, *Arch. Int. Med.* **45** 983 (June) 1930.

These fibrinogen studies were the first of a number in which deviations from the normal values of several constituents of blood, such as dextrose,<sup>5</sup> cysteine and the related mercaptans<sup>6</sup> and the lipid amino nitrogen compounds,<sup>7</sup> were described as accompanying obstructive jaundice and were considered as possibly responsible for the bleeding tendency. Subsequent work, however, indicates that they are better explained as results of damage to the liver associated with the cause of the jaundice or due to obstructive cirrhosis, being thus concomitants rather than causes of the hemorrhagic tendency.

Clinical and laboratory tests designed to detect abnormalities of the clotting mechanism were improved and demonstrated more conclusively qualitative defects, as expressed in prolonged bleeding time in the presence of stasis<sup>8</sup> and poor retractility of the clot.<sup>9</sup> Methods later appeared for more accurate estimation of the prothrombin content of the plasma,<sup>10</sup> which finally led to the discovery that the level of this component of the clotting mechanism may be depressed when bile is absent from the intestinal tract and that it is consistently and markedly lowered in subjects who show the bleeding tendency either in cases of obstructive jaundice<sup>11</sup> or in cases of biliary fistula.<sup>12</sup>

4 Linton, R. R. Relation of Blood Fibrin to Haemorrhagic Diathesis of Obstructive Jaundice, *Ann Surg* **96** 394, 1932. Lewisohn, R. Haematologic Studies as Basis for Determining Risk of Post-Operative Haemorrhage in Jaundice Patients, *ibid* **94** 80, 1931. Moss, W. Experimental Obstructive Jaundice. Its Effect on Fibrinogen and Coagulation of the Blood, *Arch Surg* **26** 1 (Jan) 1933.

5 Partos, A., and Švec, F. Gesetzmässiger Zusammenhang zwischen Blutzucker-gehalt und Blutgerinnungszeit, *Arch f d ges Physiol* **218** 209, 1927. Cannon, W. B., and Gray, H. Factors Affecting the Coagulation Time of Blood, *Am J Physiol* **34** 232, 1914.

6 Carr, J. L., and Foote, F. S. Progressive Obstructive Jaundice, *Arch Surg* **29** 277 (Aug) 1934.

7 Andrus, W. DeW., and Moore, R. A. Lipid Amino Nitrogen Content of the Blood in Diseases of the Liver and Biliary Tract, *Arch Surg* **39** 3 (July) 1939.

8 Ivy, A. C., Shapiro, P. F., and Melnick, P. The Bleeding Tendency in Jaundice, *Surg, Gynec & Obst* **60** 781, 1935.

9 Boyce, F. F., and McFetridge, E. M. A Serum Volume Test for the Hemorrhagic Diathesis in Jaundice, *J Lab & Clin Med* **23** 202, 1937.

10 (a) Quick, A. J. Stanley-Brown, M., and Bancroft, F. W. A Study of the Coagulation Defect in Hemophilia and Jaundice, *Am J M Sc.* **190** 501, 1935.

(b) Warner, E. D., Brinkhous, K. M., and Smith, H. P. Quantitative Study on Blood Clotting. Prothrombin Fluctuations Under Experimental Conditions, *Am J Physiol* **114** 667, 1936.

11 Bancroft, F. W., Kugelmass, I. N., and Stanley-Brown, M. Evaluation of Blood Clotting Factors in Surgical Diseases. *Ann Surg* **90** 161, 1929. Nygaard, K. K. Coagulability of Blood Plasma. Remarks on Technic of Its Determination, *Proc Staff Meet*, Mayo Clin **9** 151, 1934. Lewisohn<sup>4b</sup>

The general effects of jaundice or of prolonged loss of bile through external biliary fistulas on appetite and nutrition had been recognized for many years, and as long ago as 1907 Halsted advised and in his own cases carried out the collection of bile from such fistulas and its administration to patients by means of a stomach tube—a practice since become common in many clinics. A renewed interest in the importance of the presence of bile in the intestinal tract was awakened when it was shown<sup>13</sup> that in its absence absorption of the fat-soluble vitamins D and A was interfered with.

The discovery of a new accessory food factor, the fat-soluble vitamin K,<sup>14</sup> lack of which caused hemorrhagic disease in chicks, and the demonstration<sup>15</sup> that restriction of this vitamin in the diet of chicks is associated with lowered levels of the prothrombin content of the plasma suggested that a similar situation might be responsible for the prothrombin deficiency associated with obstructive jaundice.

It was soon demonstrated that this was the case in rats when bile was absent from the intestinal tract in the presence of either obstructive jaundice or biliary fistula,<sup>16</sup> since, as with other fat-soluble vitamins (A and D), bile salts are essential for absorption from the intestine. The deficiency could be corrected by administration of vitamin K and bile salts. The similar deficiency in dogs has also been demonstrated<sup>17</sup> and corrected by the use of bile salts and alfalfa extracts.

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12 Hawkins, W. B., and Whipple, G. H. Bile Fistulas and Related Abnormalities: Bleeding, Osteoporosis, Cholelithiasis and Duodenal Ulcers, *J. Exper. Med.* **62**: 599, 1935. Hawkins, W. B., and Brinkhous, K. M. Prothrombin Deficiency: the Cause of Bleeding in Bile Fistula Dogs, *ibid.* **63**: 759, 1936.

13 Greaves, J. D., and Schmidt, C. L. A. Further Experiments on Role Played by Bile in Absorption of Vitamin D in Rat, *Univ. California Publ., Physiol.* **8**: 43, 1934. On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, *Am. J. Physiol.* **111**: 492, 1935.

14 Dam, H. Haemorrhages in Chicks Reared on Artificial Diets: New Deficiency Disease, *Nature, London* **133**: 909, 1934. Almquist, H. J., and Stokstad, E. L. R. Hemorrhagic Chick Disease of Dietary Origin, *J. Biol. Chem.* **116**: 105, 1935. Dam, H. Antihemorrhagic Vitamin of Chick: Occurrence and Chemical Nature, *Nature, London* **135**: 652, 1935.

15 Dam, H., Schönheyder, F., and Tage-Hansen, E. Studies on Mode of Action of Vitamin K, *Biochem. J.* **30**: 1075, 1936.

16 Greaves, J. D., and Schmidt, C. L. A. Nature of the Factor Concerned in Loss of Blood Coagulability of Bile Fistula Rats, *Proc. Soc. Exper. Biol. & Med.* **37**: 43, 1937.

17 Smith, H. P., Warner, E. D., Brinkhous, K. M., and Seegers, W. H. Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs, *J. Exper. Med.* **67**: 911, 1938. Lord, J. W., Jr., Andrus, W. DeW., and Moore, R. A. Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals. *Arch. Surg.*, this issue, p. 585.

Widespread clinical application of these findings has confirmed both the significance of vitamin K in restoration of the plasma prothrombin to a normal level and the importance of bile salts in influencing its absorption from the intestinal tract<sup>18</sup> Various vitamin K extracts were used in the earlier series, many of them very crude as compared to the more recent compounds, but the results have been for the most part highly satisfactory

We have followed the plasma prothrombin levels in two groups of cases of disease of the biliary tract and other conditions associated with deficiencies in this clotting component In the first series 22 patients were found to have low prothrombin levels and were therefore treated with vitamin K (klotogen or cerophyl) and bile salts (bilron) By means of such therapy, plus transfusions for certain patients, we were able uniformly to bring about a cessation of hemorrhage when it was present at the time of admission or to prevent its subsequent occurrence, except in 1 patient with carcinoma involving the bile passages, who died from a massive hemorrhage from an ulcer on the posterior aspect of the duodenum which had eroded into the pancreaticoduodenal artery In this patient the prothrombin level of the plasma had previously been low but had responded promptly to appropriate therapy and at the time of the hemorrhage was normal Quite obviously the bleeding was unconnected with any prothrombin deficiency

In the course of further work on the chemical composition of the vitamin it was finally isolated<sup>19</sup> in two forms, which were shown to be 1, 4-naphthoquinones Almquist and Klose<sup>20</sup> showed that phthiocol (2-methyl, 3 hydroxy-1, 4-naphthoquinone) possesses some vitamin K activity, and, being readily available, this substance has been satisfactorily employed both orally and intravenously for the correction of prothrombin

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18 Warner, E D , Brinkhous, K M , and Smith, H P Bleeding Tendency of Obstructive Jaundice Prothrombin Deficiency and Dietary Factors, *Proc Soc Exper Biol & Med* **37** 628, 1938 Butt, H R , Snell, A M , and Osterberg, A E The Use of Vitamin K in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc. Staff Meet, Mayo Clin* **13** 74, 1938 Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, *ibid* **13** 753 1938 Rhoads, J E The Relation of Vitamin K to the Hemorrhagic Tendency in Obstructive Jaundice, with a Report on Cerophyl as a Source of Vitamin K *Surgery* **5** 794, 1939 Stewart, J D , Rourke, G M , and Allen A W Control of Postoperative Bleeding in Obstructive Jaundice, *Tr Am S A* **57** 258, 1939

19 McKee, R W , Binkley, S B MacCorquodale, D W , Thayer, S A , and Doisy, E A The Isolation of Vitamin K<sub>1</sub> and K<sub>2</sub> *J Am Chem Soc* **61** 1295, 1939

20 Almquist, H J , and Klose A A The Anti-Hemorrhagic Activity of Pure Synthetic Phthiocol *J Am Chem Soc* **61** 1611, 1939

deficiencies<sup>21</sup> The vitamin itself is believed to be 2-methyl-3, phytyl-1, 4-naphthoquinone,<sup>22</sup> and several other related compounds have been found to possess lesser degrees of vitamin K activity

By far the most potent of all compounds so far investigated is synthetic 2-methyl-1, 4-naphthoquinone, which has been shown to be several hundred times as potent as phthiocol<sup>23</sup> A recent study<sup>24</sup> indicates that its activity is as great as 30,000,000 Dam units per gram, so that it is effective in extremely minute doses When it is given by mouth, bile salts are of course essential for its absorption from the gastrointestinal tract, and Rhoads and Fliegelman<sup>25</sup> have recently reported satisfactory response to its administration by this route in 10 cases

In August 1939 we began to use this substance exclusively for the treatment of prothrombin deficiencies, and at first, while we were conducting a series of experiments on animals to determine its effect and possible toxicity when injected intramuscularly dissolved in oil, it was administered orally When our studies had demonstrated its effectiveness and lack of toxicity by intramuscular injection, we turned to this route with good effect, and since October 1 we have employed it in 38 cases, with strikingly successful results in the absence of damage to the liver Synthetic 2-methyl-1, 4-naphthoquinone is inexpensive, and intramuscular injection of this substance dissolved in corn oil is so simple and effective that we believe this to be the simplest method of administration in the treatment of prothrombin deficiencies When it is given by injection, the presence of bile salts in the intestinal tract is not necessary for its absorption, and its effect is evident within a few hours Moreover, the influence of a single injection on the concentration of plasma prothrombin may be prolonged, in many cases for at least a week As in the case of other substances with vitamin K activity, however, it would appear from both experimental and clinical work that its effectiveness may be diminished or even abolished in the presence of severe damage to the liver

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21 Smith, H P , Ziffren, S E , Owen, C A , and Hoffman, G R Clinical and Experimental Studies on Vitamin K, *J A M A* **113** 380 (July 29) 1939  
 Butt, H R , Snell, A M , and Osterberg, A E Phthiocol Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice Preliminary Report, Proc Staff Meet, Mayo Clin **14** 497, 1939

22 MacCorquodale, D W , Binkley, S B , Thayer, S A , and Doisy, E A " On the Constitution of Vitamin K, *J Am Chem Soc* **61** 1928, 1939

23 Ansbacher, S , and Fernholz, E Simple Compounds with Vitamin K Activity, *J Am Chem Soc* **61** 1924, 1939

24 Sjogren, B Die Vitamin K-Wirkung einiger Naphthochinone und Naphthochinonderivate, *Ztschr f physiol Chem* (nos 3-5) **262** 1-3, 1939

25 Rhoads, J E , and Fliegelman, M J The Use of 2-Methyl-1, 4-Naphthoquinone (A Synthetic Vitamin K Substitute) in Treatment of Prothrombin Deficiency in Patients, *J A M A* **114** 400 (Feb 3) 1940

In the preceding paper, covering animal experiments, certain points regarding the specificity of vitamin K, various aspects of its absorption and metabolism and its relation to the formation of prothrombin have been emphasized. Many of these points find confirmation in the following clinical reports. Thus chart 1 illustrates the course of a patient who was deeply jaundiced as a result of obstruction of the common duct due to carcinoma of the bile duct at a time when vitamin K therapy was not available<sup>26</sup>. Although bile salts were administered and a number of transfusions given, it is evident that there was a definite vitamin K defi-

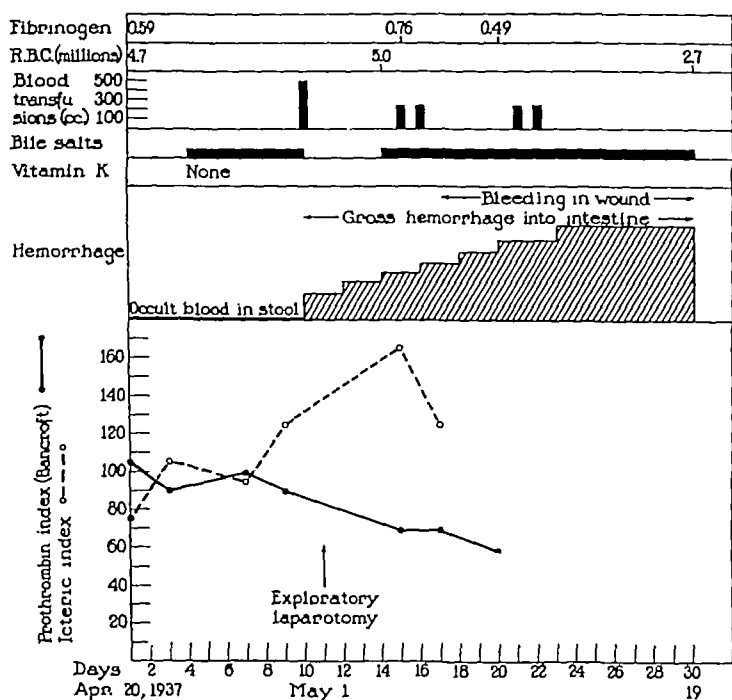


Chart 1—Data in the case of a man aged 67. Autopsy revealed carcinoma of the bile duct, with complete obstruction and hemorrhage in the viscera.

ciency in this case, with consequent lowering of the level of plasma prothrombin and severe bleeding. Fortunately, only a relatively small proportion of patients with obstructive jaundice showed the bleeding tendency even in the days before the underlying cause was known, probably, as is now known, because there is a sufficient reserve of vitamin

26 The prothrombin curve in chart 1 is in terms of the prothrombin index, with which the critical bleeding level is 70. The prothrombin curves in all other figures are in terms of per cent of normal by the test of Warner, Brinkhous and Smith.<sup>10b</sup> In this the bleeding level is 20 to 25 per cent.

K in the liver to maintain the concentration of prothrombin above the critical bleeding level for some time before it is exhausted

That vitamin K may fail to be absorbed even in the presence of bile salts is evident in the case the course of which is depicted in chart 2 This patient, with so-called nontropical sprue, was suffering from severe diarrhea, with the passage of frothy stools daily Administration of bile salts and vitamin K in ordinarily adequate amounts failed completely to elevate the level of plasma prothrombin

On the other hand, chart 3 illustrates the dramatic response to appropriate therapy in what would probably have been a fatal case prior to

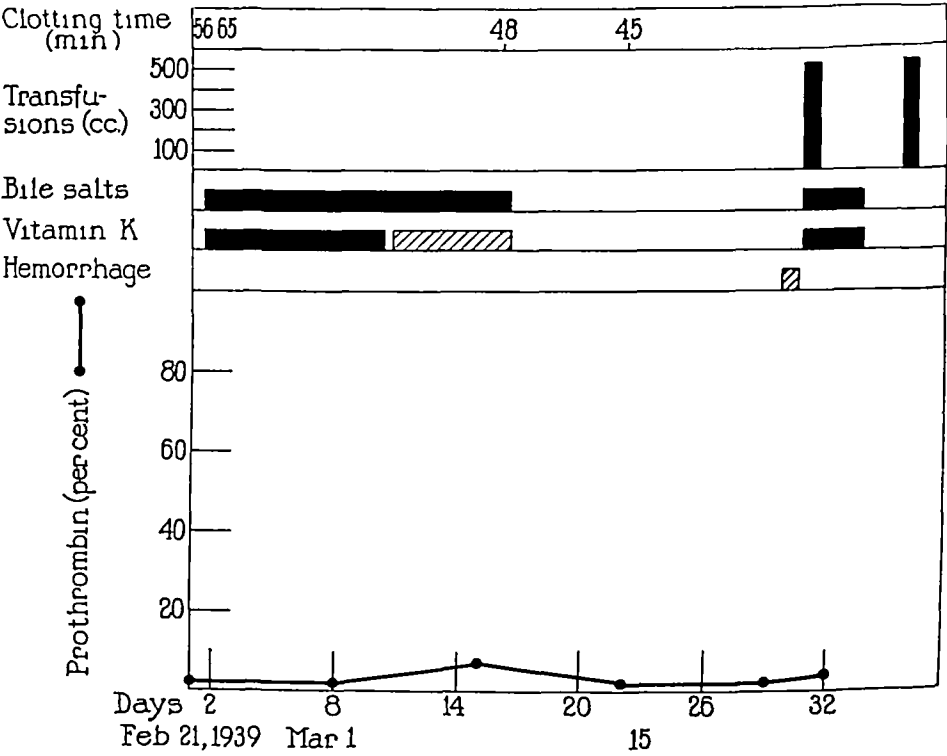


Chart 2—Data in the case of a woman aged 41 The diagnosis was nontropical sprue

recognition of the fundamental defect and of means of correcting it The patient, who had suffered for eighteen months from cicatricial stenosis of the common duct, was bleeding from the intestinal tract at the time of admission Transfusions were first administered both to restore the blood lost and as a means of supplying prothrombin directly, and at the same time adequate amounts of a vitamin K concentrate and bile salts were administered orally The hemorrhage was promptly controlled, and the plasma prothrombin was elevated within a few days to the normal level Such a response is to be expected unless some other factor, such as damage to the liver, interferes with the production of prothrombin



The depressing effect of damage to the liver on the level of plasma prothrombin can be strikingly demonstrated in animals,<sup>27</sup> and, after complete hepatectomy at least, administration of even large doses of vitamin K fails to alter materially the curve of fall. Clinical observations of the failure of response to vitamin K therapy in the presence of damage to the liver are depicted in charts 4 and 5. The patient whose course is illustrated in chart 4 was a 50 year old woman who was

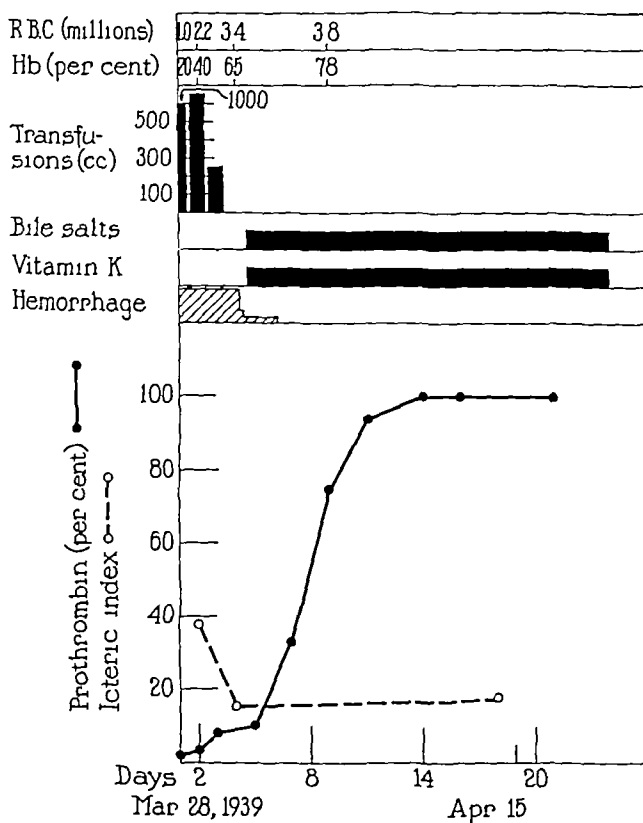


Chart 3—Data in the case of a woman aged 47. The diagnosis was inflammatory stenosis of the common bile duct.

27 Smith, H. P., Warner, E. D., and Brinkhous, K. M. Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66**: 801, 1937. Warner, E. D. Plasma Prothrombin Effect of Partial Hepatectomy, *ibid.* **68**: 831, 1938. Andrus, W. DeW., Moore, R. A., and Lord, J. W., Jr. The Effect of Hepatectomy, on the Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* **6**: 899, 1939. Lord, J. W., Jr. The Effect of Trauma to the Liver on the Plasma Prothrombin, *ibid.* **6**: 896, 1939. Warren, R., and Rhoads, J. E. The Hepatic Origin of the Plasma Prothrombin Observation After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198**: 193, 1939.

admitted to the hospital with a temperature of 40 C. She had suffered intermittently from symptoms of disease of the gallbladder for eighteen years and had been somewhat jaundiced for five weeks. Her condition was so precarious that she was treated conservatively with blood transfusions, clysis and administration of vitamin K and bile salts for four days and was then subjected to a cholecystostomy. At operation an inflammatory mass was found about the lower portion of the gallbladder and overlying the common duct. The value for plasma prothrombin, which was 25 per cent of normal on admission, rose promptly to normal after vitamin K and bile salts were administered, but after the eighth

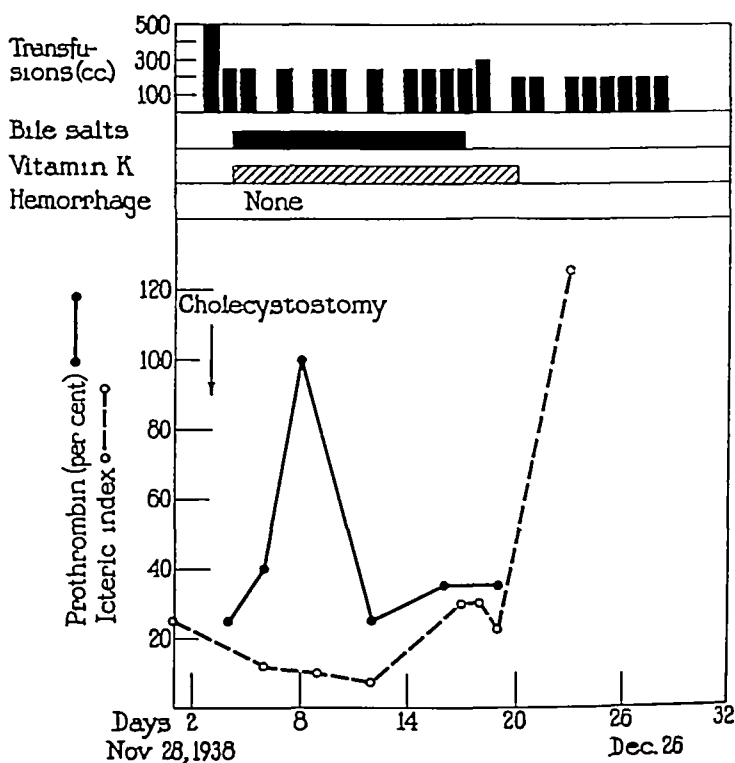


Chart 4—Data in the case of a woman aged 50. The diagnosis was stone in the common duct. Autopsy revealed thrombosis of the hepatic artery and of the portal vein. An infarct of the liver was present. There were numerous petechiae

day it suddenly fell to 25 per cent again, and it remained at about this level despite repeated transfusions and continued vitamin K therapy. The patient subsequently died, and at postmortem examination thromboses of the hepatic artery and portal vein with massive necrosis of the liver were observed. Microscopic examination of the thrombi indicated that they had been deposited at about the time that the fall in the level of plasma prothrombin occurred. The massive hepatic necrosis which followed produced an effect comparable to that seen following partial hepatectomy in animals.

A similar but less acute effect is seen in chart 5, which depicts the course of the plasma prothrombin level in a patient with severe cirrhosis of the liver. In his case the concentration of prothrombin was 70 per cent of normal before treatment with 2-methyl-1, 4-naphthoquinone was begun, but even when more than adequate doses were administered the prothrombin concentration continued to fall until it reached 48 per cent of normal. At operation the liver was found to be markedly cirrhotic and considerably reduced in size.

These 2 cases are chosen from a number illustrating the influence of damage to the liver on the level of the plasma prothrombin and the response to vitamin K, and the group as a whole suggests the significance

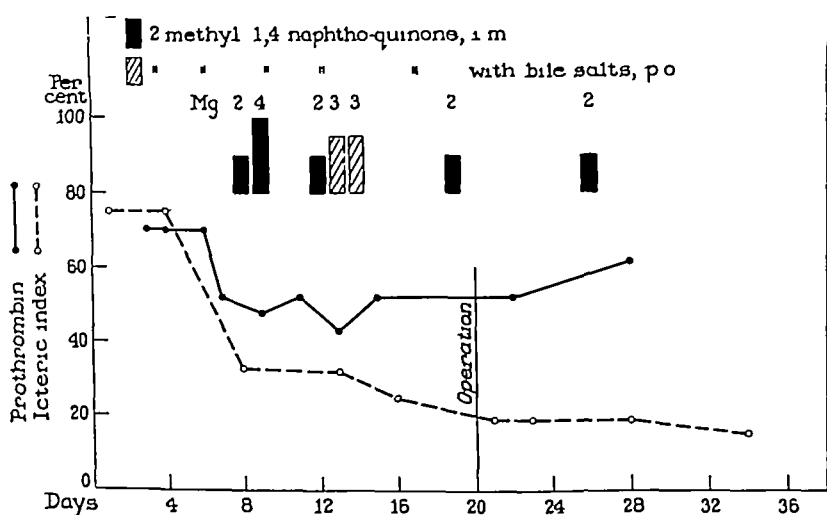


Chart 5—Data in the case of a man aged 61. The diagnosis was cirrhosis of the liver. Exploratory laparotomy was performed. The hipuric acid test revealed a value of 2.98 Gm. The galactose tolerance test showed 7.3 Gm. excreted. The bromsulfalein test showed a faint trace present after thirty minutes.

of these factors as an indication of hepatic function, at least so far as its prothrombin-forming activity is concerned. Determination of the extent to which this interpretation can be carried clinically awaits further studies, but work now in progress in this clinic lends support to this idea.

#### SUMMARY

The history of the establishment of a prothrombin deficiency as the cause of the hemorrhagic tendency associated with jaundice and of the significance of vitamin K in the production of this component of the clotting mechanism is briefly traced.

Clinical experience with crude extracts of substances containing the vitamin and later with the highly potent compound 2-methyl-1, 4-naphthoquinone is reported

Clinical cases are presented confirming various findings concerning the metabolism of vitamin K and prothrombin in animals, as reported in the preceding paper. The important role of the liver is stressed, and evidence is presented indicating that damage to this organ may depress the level of plasma prothrombin and seriously interfere with the response to vitamin K therapy

# INFLUENCE OF FUSION OF THE SPINE ON THE GROWTH OF THE VERTEBRAE

S L HAAS, MD

SAN FRANCISCO

The frequency of the operation for fusion of the spine has increased markedly in recent years, since its utilization for the treatment of scoliosis. As most fusion operations are performed on children during their active growing period, the question arises as to its influence on the growth in length of the vertebral column. If the fused spinous process should act as a brake on expansion of the corresponding bodies, the restriction of growth would be of considerable significance, particularly when one third or more of the processes are fused at one time.

In order to appreciate this investigation better it may be well to have some definite conception as to the mechanism of normal growth of the bodies of the vertebrae. It has been shown in dogs in some previous experiments that growth in length of the bodies takes place at the epiphyseal cartilaginous plates in a manner similar to that of the long bones<sup>1</sup>. It has also been shown that it is possible to stop growth of the vertebral body by destroying the epiphyseal plates or to produce deformity by injuring a part of the plate<sup>2</sup>. If fusion of the spinous processes is performed at the time of injury to the epiphyseal cartilaginous plates, deformity may be prevented<sup>3</sup>. With normal growth of the body, corresponding changes must take place in the spinous processes and in the laminae. By fusion of the spinous processes, these changes are prevented, and it is of considerable interest to know whether any secondary disturbances of growth occur in the bodies or in the intervertebral disks.

It is believed that growth of the vertebrae in man takes place similarly to that in the dog, in spite of the claims of Schmorl and his followers to the contrary. The reason for this discrepancy of opinion may be the fact that in man the growth of the spine is distributed over fifteen to twenty years. The growth in man of each vertebra over this long period is very small, and therefore there is little demand for a highly

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From the Surgical Laboratory, the Stanford School of Medicine.

1 Haas, S. L. Growth in Length of the Vertebrae, *Arch Surg* **38** 245 (Feb) 1939.

2 Haas, S. L. Experimental Production of Scoliosis. *J Bone & Joint Surg* **21** 963 (Oct) 1939.

3 Haas, S. L. The Prevention of Deformity of the Spine by Vertebral Fusion. *J Bone & Joint Surg* **22** 157 (Jan) 1940.

differentiated epiphysial cartilaginous plate. The columns of cartilage in the vertebral bodies of man are rather irregular and are narrow, but they are adequate for purposes of slow growth. On the contrary, for the dog the period of growth is only nine months, and there is a demand for rapid growth, so that there is of necessity a more highly specialized epiphysial cartilage plate. The columns of cartilage are longer and more regular, approaching more nearly those of the long bones, in which growth is rapid.

In an effort to determine the effect of fusion of the vertebrae on growth of the spine, a series of experiments were performed on growing dogs in which the vertebrae were fused by either the Hibbs or the Albee method. Wire markers were placed in the operative area to indicate whether any changes took place during the growth of the animal. In another group of experiments, in addition to the fusion of the spinous processes, the bodies of the vertebrae were exposed through an abdominal approach, and markers were placed in the bodies and epiphyses of the vertebrae for comparative studies of growth.

At the beginning of the experiments roentgenograms were taken for record showing the position and distance apart of the markers. Roentgenograms were also taken at the end of the experimental period to show the final position of the markers. The distances between the markers were measured and compared with those at the time of operation to determine the amount of growth that took place between the markers during the period of observation. Comparative studies were made between growth in the spine and growth in the vertebral bodies. The study of the gross specimens showed the changes in shape of the spine. The cut specimens were studied for changes in the epiphysial plates, the epiphyses, the bodies and the intervertebral disks.

There were 22 experiments (1) five Hibbs fusions, (2) twelve Albee fusions, (3) three combination Hibbs fusions with placing of markers in the bodies of the vertebrae, and (4) two combination Albee fusions with placing of markers in the bodies of the vertebrae.

#### HIBBS TYPE OF SPINAL FUSION

There were 5 operations in this series, in which the spinous processes were fused by various modifications of the Hibbs operation.

*EXPERIMENT 1—Dog 1, age, 4 months, duration of experiment, twenty days*

*Operation*—With ether anesthesia and under sterile conditions an incision was made over the lumbar spinous processes. The spinous processes were exposed, and the muscles were stripped off subperiosteally from the spinous processes of three vertebrae. The spinous processes were interlocked with each other. The articular facets were not destroyed.

*Gross Observations*—There was considerable osseous proliferation, considering the short time since the operation. There was a fair amount of fixation in the fused area. The bodies bulged slightly anteriorly.

*Growth*—The duration of the experiment was too short to show any disturbance in growth

EXPERIMENT 2—Dog 4, age, 3 months, duration of experiment, thirty-four days

*Operation*—On March 19, 1935, with the dog under ether anesthesia, an incision was made over the lumbar spinous processes. The muscles were deflected to either side subperiosteally. The articular facets were not destroyed. The spinous processes were interlocked with each other, and bone was raised from the laminae and brought into contact with the laminae from above and below. Two wire markers were placed in the spinous processes. The wound was closed in layers.

*Gross Observations*—There was a little fixation of the spine. There was some proliferation of bone between the spinous processes. The articular facets showed no changes, as they were not destroyed. There were no changes in the bodies, and the epiphyseal cartilaginous plates appeared normal.

*Growth*—There was a slight amount of rigidity in the operative area of the spine. There was a slight increase in distance between the markers. Very little change was seen in the intervertebral disk or the epiphyseal cartilaginous plates.

EXPERIMENT 3—Dog 5, age, 3 months, duration of experiment, two hundred and five days

*Operation*—On March 19, 1935, incision was made over the lower part of the thoracic and the lumbar region of the spine. The spinous processes from the twelfth thoracic to the fourth lumbar were exposed. The muscles were stripped from either side. The articular facets were exposed but not destroyed. Sections of bone were raised from the laminae and placed over the facets. The spinous processes from the twelfth thoracic to the fourth lumbar were made to interlock with each other. Wire markers were attached to the spinous processes, after which the wound was closed in layers.

*Gross Observations*—There was firm fixation in the operative area of the spine. The spinous processes were connected with new bone. The articular facets were covered with osseous tissue. The articular cartilages of the facets persisted but were thin. When the bodies of the vertebrae were cut through, the epiphyseal cartilaginous plates were observed to be narrow, and some appeared almost completely closed. There was an anterior bulging of the bodies.

*Growth*—The markers in the operative area of the spine had separated almost as much as the body had grown (fig. 1). This can be explained by the fact that until fusion is firm and soft callus yields, and there is a pulling apart or stretching of osteoid tissue in the operative area. When ossification is complete, there is no further yielding of the tissue and separation of the markers. There was some compression of the intervertebral disk, which takes place when the fused vertebrae tend to prevent expansion of the bodies in the operative area (fig. 2).

EXPERIMENT 4—Dog 6, age 4½ months, duration of experiment, one hundred and sixty days

*Operation*—On July 9, 1935, an incision was made over the lower part of the thoracic and the lumbar region. The spinous processes were exposed and the muscles deflected to either side subperiosteally. Five articular facets were destroyed on the right side and the spinous processes were made to interlock with each other. Wire markers were placed in the vertebrae at either end of the operative area. The wound was closed in layers and a plaster was applied.

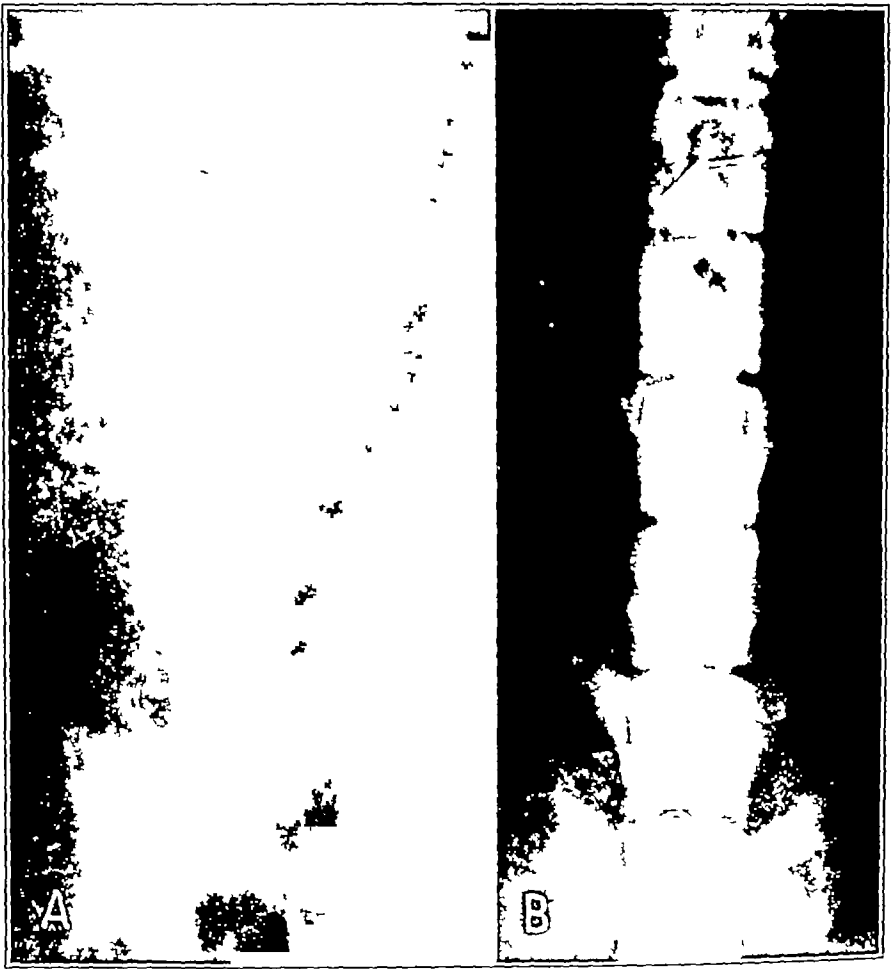


Fig 1 (experiment 3, dog 5, Hibbs type of fusion, age, 3 months, duration of experiment, two hundred and five days, anteroposterior views) —Roentgenograms, (A) at the time of operation and (B) at the end of the experimental period, for comparison, showing that separation of markers is almost equal to body growth. Separation continues until fusion is firm enough to resist body growth. The intervertebral disks are narrowed only slightly.

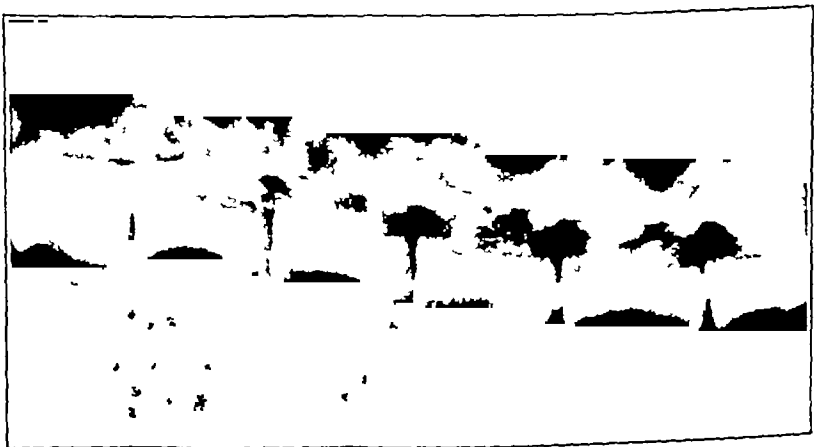


Fig 2 (dog 5, age, 3 months, duration of experiment, two hundred and five days) —Lateral view, showing a little narrowing of the intervertebral disk and a little tendency to anterior bowing. It is only after fusion is firm that the inhibiting force against growth manifests itself.



*Gross Observations*—There was very firm fusion in the operative region of the spine. The articular facets that had been destroyed were firmly fused. Those that had not been destroyed showed very thin articular cartilages. The epiphyseal plates could be made out but in some places appeared ossified.

*Growth*—The markers in the spinous processes had separated about the same amount as the bodies had increased in length. There was no tendency to lordosis or scoliosis of the spine. The disks were compressed about half their normal width. The epiphyseal cartilaginous plates showed some evidence of ossification.

EXPERIMENT 5—Dog 7, age, 5 months, duration of experiment, twenty-six days

*Operation*—On July 16, 1935, an incision was made over the lower part of the thoracic and the lumbar region of the spine. Five spinous processes were exposed, and the muscles were deflected to either side. Three of the articular facets were destroyed, and bone was thrown down from the laminae on the remainder. The spinous processes were made to interlock with each other, after which the wound was closed in layers.

*Gross Observations*—There was beginning fusion of the spinous processes and laminae in the operative region, with definite fixation of the spine. The articular facets which had been destroyed showed early signs of fusion. The epiphyseal cartilaginous plates appeared normal. There was a little tendency to anterior bulging of the bodies.

*Growth*—At the end of twenty-six days no significant changes were made out.

#### CONCLUSION ON HIBBS TYPE OF FUSION

After the Hibbs type of spinal fusion it was found that the markers placed in the spinous processes operated on had separated in some experiments almost as much as the body had grown. This separation was due to the fact that as the bodies of the vertebrae grow in length the soft callus in the spinous processes operated on yields to the growing forces. As soon as the callus becomes firm there is no more separation of the markers. There is some narrowing of the intervertebral disk and of the epiphysis, particularly at the posterior parts, but it is not marked unless there is an experimental period of considerable length. This narrowing of the disk and epiphyses is due to compression, which results when the fused spinous processes prevent the normal longitudinal expansion of the growing bodies of the vertebrae.

#### ALBEE TYPE OF SPINAL FUSION

In this group there were 12 experiments, in which the spine was fused by the Albee method or by some modification of it.

EXPERIMENT 6—Dog 1 age 6 months, duration of experiment three hundred and fifty days

*Operation*—On Oct. 20, 1936, an incision was made from the first to the fourth lumbar spinous process. The muscles were deflected subperiosteally from the spinous processes. A bone graft was removed from the tibia and placed in the split spinous processes of the lumbar vertebrae. Wire markers were placed in the spinous

beginning ossification. The disks were thinner posteriorly than anteriorly, and there was bowing forward of the bodies of the vertebrae.

*Growth*—The markers, which were attached to the graft, were prevented from separating. There was a considerable increase in size of the bodies of the vertebrae. The disks were moderately compressed. The epiphysal cartilaginous plates showed signs of ossification about the periphery. The last lumbar vertebra showed a wedge-shaped disk, most likely caused by extreme pressure posteriorly.

EXPERIMENT 16—*Dog 11, aged, 4 months, duration of experiment, two days (dog died)*

*Operation*—On June 23, 1937, an incision was made over the lumbar spinous processes. Four of the processes were exposed and the muscles stripped off subperiosteally from both sides. A bone graft was removed from the femur and placed alongside the denuded processes. The articular facets were destroyed. The wound was sutured in the usual manner, and a plaster cast was applied.

*Gross Observations*—The grafts were found in place, and the blood clots were beginning to organize.

*Growth*—There were no changes at this early period.

EXPERIMENT 17—*Dog 12, age, 4 months, duration of experiment, one hundred and eleven days*

*Operation*—On June 23, 1937, an incision was made over the lumbar spinous processes. Dissection was carried down the processes, and the muscles were stripped subperiosteally from either side. A bone graft removed from the femur was anchored to the lower spinous process with a wire. A wire marker was placed on the upper spinous processes but not fastened to the graft. The articular facets were curetted on one side.

*Gross Observations*—The bone graft was well united to the spinous processes, producing firm fusion. The destroyed articular facets on one side showed fusion. The epiphysal cartilaginous plates could be made out but were a little thinner than normal in the fused area, and some showed beginning ossification. The epiphyses were wedge shaped, being broader anteriorly. The intervertebral disks were not changed, but there was definite anterior bowing of the bodies.

*Growth*—The markers had separated, but much less than the body had grown. There was a definite anterior bulging of the bodies of the vertebrae. The spinal canal was widened. The disks were compressed and at the posterior end were narrower, and in some places there was almost bony fusion. The epiphysal cartilaginous plates showed evidence of ossification posteriorly, and the epiphyses were narrower posteriorly.

#### CONCLUSION ON ALBEE TYPE OF FUSION

There is more rapid fusion with the Albee type of operation in which a bone graft is inserted into the spinous process than in the Hibbs type of operation. Consequently, there is less separation of the markers in the spinous process than is observed with the Hibbs type. There is also a greater disproportion between separation of the markers and body growth with the Albee than with the Hibbs type. There are more marked changes in the intervertebral disk and in the epiphyses



Fig 3 (experiment 14, dog 9, age,  $4\frac{1}{2}$  months, duration one hundred and twenty-six days, Albee type of fusion) —Anteroposterior roentgenograms showing much greater growth of the body than separation of the markers. Fusion took place more quickly than with the Hibbs type of operation, so that the markers in the spinous processes did not separate so much as the body of the vertebrae increased in size. After fusion the resistance to expansion causes compression of the intervertebral disk and anterior bowing of the bodies.

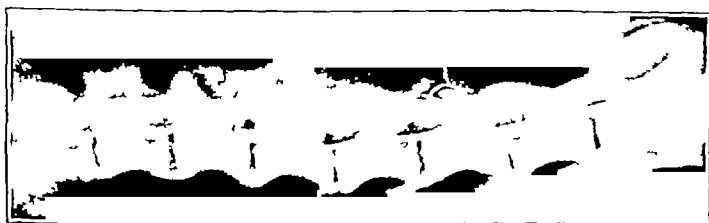


Fig 4 (experiment 14 dog 9 age  $4\frac{1}{2}$  months duration of experiment, one hundred and twenty-six days) —The lateral view shows the anterior bulging of the bodies with a tendency to lordosis. The fused spinous processes offer resistance to expansion longitudinally and the body growth protrudes toward the place of least resistance which is anteriorly in the direction of the abdominal cavity. Note the compression of the disk which is greater posteriorly. In the anteroposterior view the narrowing appears to occupy the entire disk while in fact, as is shown in the lateral view, it is wide anteriorly and narrow posteriorly.

beginning ossification. The disks were thinner posteriorly than anteriorly, and there was bowing forward of the bodies of the vertebrae.

*Growth*—The markers, which were attached to the graft, were prevented from separating. There was a considerable increase in size of the bodies of the vertebrae. The disks were moderately compressed. The epiphysal cartilaginous plates showed signs of ossification about the periphery. The last lumbar vertebra showed a wedge-shaped disk, most likely caused by extreme pressure posteriorly.

EXPERIMENT 16—*Dog 11, aged, 4 months, duration of experiment, two days (dog died)*

*Operation*—On June 23, 1937, an incision was made over the lumbar spinous processes. Four of the processes were exposed and the muscles stripped off subperiosteally from both sides. A bone graft was removed from the femur and placed alongside the denuded processes. The articular facets were destroyed. The wound was sutured in the usual manner, and a plaster cast was applied.

*Gross Observations*—The grafts were found in place, and the blood clots were beginning to organize.

*Growth*—There were no changes at this early period.

EXPERIMENT 17—*Dog 12, age, 4 months, duration of experiment, one hundred and eleven days*

*Operation*—On June 23, 1937, an incision was made over the lumbar spinous processes. Dissection was carried down the processes, and the muscles were stripped subperiosteally from either side. A bone graft removed from the femur was anchored to the lower spinous process with a wire. A wire marker was placed on the upper spinous processes but not fastened to the graft. The articular facets were curetted on one side.

*Gross Observations*—The bone graft was well united to the spinous processes, producing firm fusion. The destroyed articular facets on one side showed fusion. The epiphysal cartilaginous plates could be made out but were a little thinner than normal in the fused area, and some showed beginning ossification. The epiphyses were wedge shaped, being broader anteriorly. The intervertebral disks were not changed, but there was definite anterior bowing of the bodies.

*Growth*—The markers had separated, but much less than the body had grown. There was a definite anterior bulging of the bodies of the vertebrae. The spinal canal was widened. The disks were compressed and at the posterior end were narrower, and in some places there was almost bony fusion. The epiphysal cartilaginous plates showed evidence of ossification posteriorly, and the epiphyses were narrower posteriorly.

#### CONCLUSION ON ALBEE TYPE OF FUSION

There is more rapid fusion with the Albee type of operation in which a bone graft is inserted into the spinous process than in the Hibbs type of operation. Consequently, there is less separation of the markers in the spinous process than is observed with the Hibbs type. There is also a greater disproportion between separation of the markers and body growth with the Albee than with the Hibbs type. There are more marked changes in the intervertebral disk and in the epiphyses

and epiphysial plates, because with earlier firm fusion of the spine there are greater hindrance of expansion of the bodies by growth and more compressive force. The bodies, being hindered from longitudinal expansion, tend to project anteriorly toward the place of least resistance, normally away from the fixed part of the spine.

#### COMBINATION HIBBS FUSION AND PLACING OF MARKERS IN BODIES OF VERTEBRAE

In this series there were 3 experiments in which the Hibbs type of spinal fusion was performed at one operation and, after an interval to allow healing of the wound, a second operation was performed, in which the bodies of the vertebrae were exposed through an abdominal incision

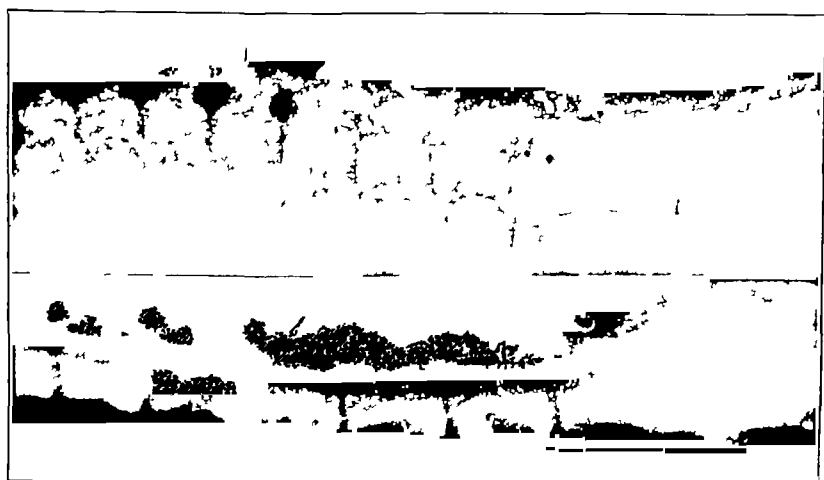


Fig 5 (experiment 18, dog 7, age,  $3\frac{1}{2}$  months, Hibbs fusion with markers in the bodies of the vertebrae, duration of experiment, one hundred and fifty-one days) —The lateral views show the markers in the spinous processes and in the bodies. The markers in the area of fusion have separated almost as much as the body has grown. Notice how the markers in the bodies have separated according to the presence of one or more intervening epiphysial cartilage plates between them. There is very little narrowing of the intervertebral disk and very little tendency to anterior bowing of the bodies. The roentgenogram at the top was taken before operation, that at the bottom, after operation.

Markers were placed in the bodies to serve as a means of determining changes in growth to compare with markers in the spinous processes operated on.

*EXPERIMENT 18—Dog 7 age  $3\frac{1}{2}$  months, duration of experiment, one hundred and fifty-one days*

*Operation First Part—*On March 3 1936 an incision was made over the spinous processes of the lower lumbar vertebrae. The processes were exposed

and the muscles deflected to either side subperiosteally. The articular facets of three of the vertebrae were destroyed. Sections of bone were thrown over the facets from the laminae. The spinous processes were not interlocked. Markers were placed at either end of the operative area and on the spinous processes above and below those operated on. The wound was closed in layers, and plaster was applied.

*Operation, Second Part*—On March 25, through a midabdominal incision, the intestines were exposed and walled off until the posterior abdominal wall was exposed. The abdominal aorta and vena cava were exposed and gently retracted to one side. Care was taken not to injure the ureter. The periosteum was incised, and the desired portion of the bodies of the vertebrae was exposed. A wire marker was placed in the body of three vertebrae and in the middle one. An additional marker was placed in the epiphysis. The gauze packs were removed, and the abdominal incision was closed in layers.

*Gross Observations*—There was fairly firm fusion but not complete bony union of the spinous processes. There was beginning ossification of some of the facets. There was no gross narrowing of the bodies. The epiphysal cartilaginous plates were present and were a little thin but they differed little from those opposite the nonfused area. The epiphysis did not show any change. The disks were a little narrower than normal posteriorly. The bodies showed anterior bowing.

*Growth*—There had been a greater growth of the body than separation of the markers in the spinous processes. There was not much compression of the disks. There was little lordosis. The markers in the bodies showed separation, the amount depending on the number of intervening epiphysal plates (fig 5). As far as could be determined, there was just as much growth of the bodies in the fused areas as outside.

EXPERIMENT 19—*Dog 10, age, 3½ months, duration of experiment, eighty-four days*

*Operation, First Part*—On March 10, 1938, an incision was made in the midabdominal line, the peritoneum was incised with exposure of the intestines, which were walled off with gauze. With careful avoidance of the large vessels and ureters, the bodies of the lumbar vertebrae were exposed. After an incision had been made through the periosteum, it was stripped off to either side, the epiphysal plate being exposed. The epiphysal cartilaginous plate of the middle vertebrae was injured, and markers were placed in the epiphysis. In the lower vertebra a hole was bored in the body and a marker placed in the hole. In the upper vertebrae a marker was placed in the body and in the epiphysis.

*Operation, Second Part*—On March 25 an incision was made over some of the spinous processes, which were exposed. The muscles were deflected to either side subperiosteally, after which the articular facets were destroyed, bone was thrown up from the laminae and the spinous processes were made to interlock. The wound was then closed in layers.

*Gross Observations*—There was firm fusion of the spinous processes, and the articular facets appeared fused. The epiphysal cartilaginous plates were normal in structure. The intervertebral disks were thinner posteriorly and broader on the anterior surface. There was no definite bulging of the bodies anteriorly.

*Growth*—Body growth was greater than separation of the markers except where the body had been injured or the epiphysal plate destroyed. All the intervertebral disks were narrower, and there was a tendency for bony bridging across

one disk. There was not much tendency to kyphosis, in spite of the fact that there was extensive destruction of the epiphyseal plate and body.

**EXPERIMENT 20—Dog 11, age,  $3\frac{1}{2}$  months, duration of experiment, three hundred and fifty-one days**

**Operation, First Part**—On March 14, 1938, through a mid-abdominal incision, the viscera were exposed and walled off. Care was taken not to injure the large vessels, and the bodies of the vertebrae were exposed. The periosteum was then incised and stripped off over a small area so that the epiphyseal cartilaginous plates could be identified. Markers were placed in the bodies of three vertebrae. In the two lower vertebrae sections of bone were turned up from the bodies and brought into contact with one another over the intervertebral disk. The packing was removed and the abdominal wall closed in layers.

**Operation, Second Part**—On March 25 an incision was made over four spinous processes, after which the muscles were stripped off subperiosteally from either side. The articular facets were destroyed and the spinous processes made to interlock with each other. The wound was closed in layers.



Fig 6 (experiment 20, dog 11, age,  $3\frac{1}{2}$  months, Hibbs fusion in conjunction with bridging between the bodies of the vertebrae, duration of experiment, three hundred and fifty-one days) —Notice that besides the Hibbs fusion of the spinous process there is a bony bridge between the bodies of two vertebrae. This acts as an accessory supporting measure to prevent deformity besides decreasing longitudinal expansion of the bodies of the vertebrae.

**Gross Observations**—There was fairly firm fusion of the spine but not complete osseous bridging between the spinous processes. The articular facets were irregular in form, with some proliferation about them but no osseous fusion. Some of the disks appeared narrower posteriorly. The epiphyseal cartilaginous plates were ossified. There was no anterior bulging of the bodies.

**Growth**—There was an anterior bony bridging between the bodies where the sections of bone had been thrown across the disk (fig 6). This caused a considerable hindrance of growth. The bodies outside this area had increased normally and to a greater extent than had separation of the markers in the fused area. There was no anterior bulging in the fused area as it was prevented by the anterior bridge of bone between the bodies of the vertebrae. The epiphyseal cartilaginous plates in the operative as well as in the nonoperative area were ossified.

# CONCLUSION ON COMBINATION HIBBS FUSION AND PLACING OF MARKERS IN THE BODIES OF THE VERTEBRAE

The combination operations gave a clearer idea of the relative amount of growth of the bodies and separation of the markers in the spinous processes operated on. The findings were practically the same as with the simple Hibbs fusion, in that separation of the markers in the fused spinous processes proceeded with growth of the bodies until union was firm, after which growth was almost entirely confined to the bodies. There was only a moderate amount of compression of the disk and bodies posteriorly.

## COMBINATION OF ALBEE FUSION OF SPINE AND PLACING OF MARKERS IN BODIES

There were 2 operations in which the Albee type of fusion was performed and at a later date markers were placed in the bodies of the vertebrae through an abdominal approach.

*EXPERIMENT 21—Dog 8, age, 3½ months, duration of experiment, one hundred days*

*Operation, First Part*—On March 3, 1938, the spinous processes of three lumbar vertebrae were exposed through an incision in the lumbar region. The muscles were deflected to either side, and the spinous processes were split in half. A bone graft removed from the femur was placed between the split processes. One pair of articular facets were destroyed below this area. Markers were placed at either end and on one of the spinous processes below the last vertebrae operated on. The wound was closed in layers, and plaster was applied.

*Operation, Second Part*—On March 21, through an abdominal incision, after retraction of the viscera the bodies of the lumbar vertebrae were exposed. Markers were placed in the bodies of three vertebrae and an additional marker in the epiphysis of the lower vertebrae. The wound was closed in layers.

*Gross Observations*—There was firm fusion of the spinous processes. The articular facets were fused on one side. The epiphysal cartilaginous plates showed no gross changes. The epiphyses were wedge shaped, being broader anteriorly. The intervertebral disks were thin posteriorly and broad anteriorly. The bodies of the vertebrae bowed anteriorly.

*Growth*—The markers in the spinous processes, not being attached to the graft, separated until fusion was firm. The markers in the bodies had separated, except those that had no intervening epiphysal plate. There was bulging forward of the bodies, with greater growth anteriorly (fig 7). The disks were narrowed posteriorly. The epiphysal plates were not so prominent in the fused area as outside it.

*EXPERIMENT 22—Dog 9, age, 3½ months, duration of experiment, two hundred and sixty-one days*

*Operation, First Part*—On March 7, 1938, through a midline abdominal incision, the intestines were exposed and walled off. The bodies of the vertebrae were then exposed and the periosteum incised. Markers were placed in the bodies of three vertebrae and in two epiphyses of adjoining vertebrae.



*Operation, Second Part*—On March 25 an incision was made over the lumbar spinous processes. The spinous processes were exposed and the muscles deflected subperiosteally to either side. Several bone grafts were removed from the upper end of the femur and wedged into the spinous processes. Markers were placed in the base of the spinous processes at either end and looped over the middle of the graft. A plaster spica was applied.

*Gross Observations*—There was osseous fusion of the spinous processes. The articular facets showed no gross changes. The epiphysial cartilaginous plates had fused. There were no gross changes in the disk and bodies, and the bodies did not project forward.

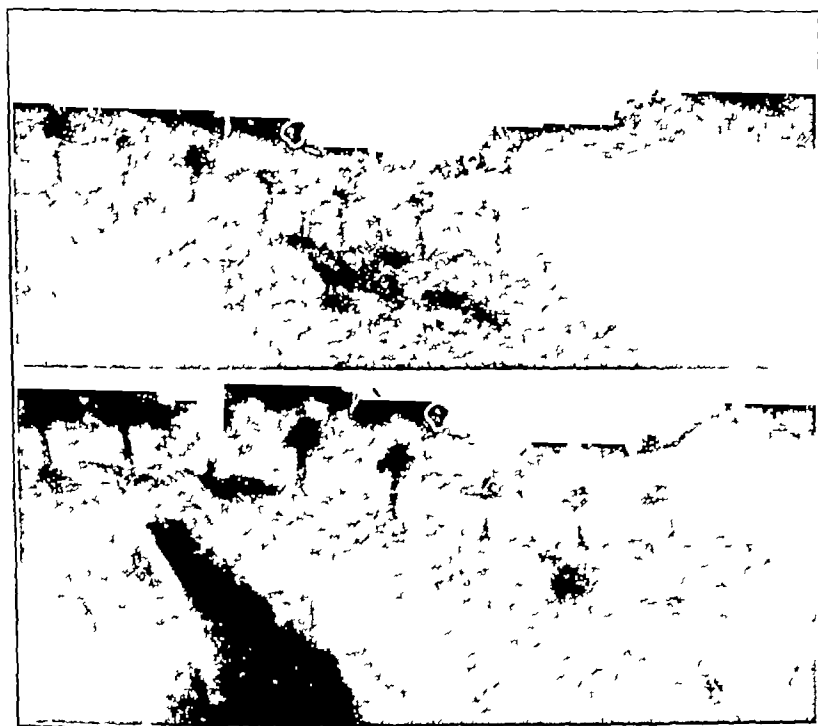


Fig 7 (experiment 21, dog 8, age,  $3\frac{1}{2}$  months, Albee fusion with markers in the bodies of the vertebrae, duration of experiment, eighty-four days) —Lateral views. The markers in the fusion area have separated much less than the body has grown. Body growth is being interfered with, as is shown by the narrowing of the intervertebral disk posteriorly and the lordosis of the bodies as they bulge anteriorly toward the place of least resistance. The growth between the markers in the bodies varies with the presence of intact epiphysial cartilage plates between them. Notice the wide anterior part of the intervertebral disk and the narrow posterior portion. The roentgenogram at the top was taken before operation, that at the bottom, after operation.

*Growth*—The markers in the spines had separated very little. There was much greater growth of the bodies. The epiphysial plates were fully ossified. The intervertebral disks had been compressed posteriorly, but the bulging anteriorly was not very marked.

CONCLUSION ON COMBINATION ALBEE FUSION AND PLACING  
OF MARKERS IN BODIES OF VERTEBRAE

This series of combination Albee experiments substantiate the findings with the simple Albee fusion operations. They give a clearer conception of the changes in growth in the bodies of the vertebrae. It is seen that whenever there is an epiphysial cartilaginous plate between two markers there is a separation of the markers, due to the fact that longitudinal growth takes place at the epiphysial cartilaginous plate. The inhibiting forces of fusion of the spine cause narrowing of the epiphysis posteriorly and compression of the posterior part of the intervertebral disk and bowing of the bodies anteriorly.

COMMENT

It is important to keep in mind that in the dog the period of growth is limited to between eight and nine months, so that in the animal operated on at 2 months of age there are approximately about two hundred and ten days more of growth.

With the Hibbs type of operation the markers in the fused spinous processes separated almost as much as the bodies increased in size or the markers in the bodies separated. The markers in the fused spine separated because it took a considerable period for the spinous processes to become firmly fused and not be subjected to the traction force of the growing vertebral bodies. In other words, the growing vertebral bodies served as a lengthening apparatus during the period in which the callus was soft. Just as soon as fusion was firm in the spinous processes, there was no yielding in the fused spine to the growing forces of the bodies, and no further separation of the markers took place. When fusion was firm in the spinous processes, the reverse took place, and the fused spine exerted a hindering force on body growth. This is evidenced by the compression of the disk, the bulging anteriorly of the bodies, the tendency to wedging of the epiphysis and the premature ossification of the epiphysial plates.

With the Albee type of fusion there was much less separation of the markers in the spinous process. This was due to an earlier firm fusion of the spines, and on that account there was less chance for growth of the body to expand the fused area. Just how much disturbance in body growth takes place is difficult to evaluate. There is considerable evidence that the inhibitory forces are strong, as evidenced by a tendency for the bodies to bend anteriorly. There are also thinning of the disk and ossification, especially at the posterior part of the disk. The epiphysis is wedge shaped with the apex posterior. The epiphysial plates are prematurely ossified. It is this wedging of the bodies with narrowing and ossification of the disk at the posterior end that give the

characteristic picture of narrowing of the intervertebral disk, which may be seen in the anteroposterior roentgenogram of any fused spine. On gross examination, definite widening and bulging of the disk anteriorly are seen in these same specimens, which in the roentgenogram appear narrow because of compression of the posterior portion.

With the Albee type of operation, if the markers are attached to the graft there is no separation of the markers, because there is no interstitial growth in a graft. The grafted region may be increased to some extent if bone is added to either end by a proliferation of osseous tissue adjoining the grafted area.

In the series of experiments in which markers were attached to the spinous process and at a second operation on the same animal the markers were placed in the bodies through an abdominal incision, a somewhat clearer idea was obtained of the body growth and a better opportunity was provided for comparative study of changes in the bodies and in the fused spinous processes. It was seen that the markers in the spinous processes separated up to the time of firm fusion of the spinous processes. The body markers separated as long as body growth took place. It is difficult to determine the exact amount of inhibition in body growth after firm fusion of the spinous processes, but there must have been a considerable hindering force at work after this firm fusion occurred, because the bodies tended to bulge anteriorly, and lordosis took place. There was also compression of the intervertebral disk, wedging of the epiphysis and changes in the epiphysial cartilage plates indicative of restriction to longitudinal expansion.

Unfortunately, it is impossible to correlate the findings in animals with what takes place in human beings, because of the long period (up to eighteen years) of growth in man as compared with the short growth period (about nine months) for animals. One would expect more inhibition of growth and more changes in the disk and bodies, because there is a much longer period for these forces to work, and the amount of normal growth is greater in man.

Many interesting questions arise from the clinical as well as from the experimental side. Although it is not within the scope of this paper to take up these problems, there is sufficient clinical evidence to show a corrective or preventive property after fusion. Secondary compensatory increase in growth outside the fused area is one of the other problems that needs investigation. The effect of fusion of the spine on a very young growing person needs careful study. It is possible that in some cases it may aggravate rather than decrease the deformity. Therefore, it is important to select the proper region of the spine, the correct age for fusion and the proper number of vertebrae to fuse. It is possible that if more attention is paid to these details better results may be obtained in the future treatment of scoliosis.

## CONCLUSIONS

Fusion of the spinous processes in animals causes definite changes in the growing vertebral bodies. Although body growth goes on, there are inhibitory forces at work, as is evidenced by the tendency of the bodies to bulge anteriorly, the tendency to lordosis, the tendency to compression of the intervertebral disk, especially posteriorly, and the tendency to premature ossification in the epiphysial cartilaginous plates. Advantage may be taken of distortion and inhibitions of growth caused by fusion of the spinous processes for the correction of existing deformities of the growing spine—in cases of tuberculosis, to correct the kyphosis by the production of lordosis. In cases of scoliosis, aside from the usual fixation after correction, it is possible that fusion can be produced outside the curve or in certain parts of an existing curve to exert a corrective influence or to prevent increase of early scoliosis more satisfactorily than is possible at present. The intra-abdominal approach, with fusion between the bodies or destruction of the epiphysial cartilaginous plate, if found practical, may help solve some of the problems of scoliosis, hemivertebrae and fracture and disease of the vertebral bodies.

# EXTENSIVE PLEXIFORM NEUROFIBROMATOSIS OF THE SCALP AND PINNA

RUSSELL MEYERS, M D

BROOKLYN

The purpose of this paper is to describe a recent experience with a rare type of benign tumor of the scalp, to narrate its life history with particular reference to alterations in its histologic characteristics and to describe the operative procedure employed in an attempt to improve the disfigurement resulting from the tumor

## REPORT OF A CASE

A 21 year old clerk was admitted to the neurosurgical service of the Kings County Hospital on Nov 16, 1938 His chief complaints referred to a marked redundancy of the scalp overlying the left side of the head and to a downward sagging of the left ear Except that the patient's mother had had a convulsive disorder during childhood, the family history was noncontributory The past personal history indicated that measles had been the only childhood exanthematous disease contracted by the patient His health otherwise had been excellent until the onset of the present illness, during his ninth year At this time the first evidences of a curvature of the upper part of the thoracic portion of the spine were noted During the ensuing year this condition advanced insidiously Examination at one of the local hospital dispensaries revealed in addition to kyphoscoliosis of the thoracic portion of the spine a tumor of the scalp, just above the left ear This was described as equal in area to a 25 cent piece and feeling "like a mass of small glands" The patient was referred into the hospital for further study on Sept. 13, 1928, and there clinical, laboratory and roentgen examinations failed to demonstrate the existence of glandular, enteric, osseous or pulmonary tuberculosis Osteomyelitis of the spine similarly appeared capable of being ruled out The films of the skull revealed a zone of rarefaction approximately  $\frac{3}{4}$  inch (1.9 cm) in diameter and corresponding in position to the mass on the scalp Late in September, an operation was carried out, with excision of the tumor of the scalp and rongeur-ing away of the immediately subjacent portion of the left vault A microscopic specimen of the scalp tissue removed at this time (fig 1) was made available through the courtesy of Dr Leo Davidoff A histologic diagnosis of fibroma of the scalp was made The record bore no information with reference to the pieces of bone removed

During the next three years, efforts to improve the kyphoscoliosis by use of plaster of paris body casts and spinal braces were carried out but were apparently ineffective Therefore, spinal fusion was performed in June 1931 the spine being fixed from the sixth thoracic to the second lumbar vertebra inclusive After

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From the Neurosurgical Service of the Kings County Hospital Dr E Jefferson Browder, Director

the operation the patient's general health remained satisfactory except that his nutritional state required special attention. No advance in the kyphoscoliosis was noted from this time on.

In July 1933, however, a lumpy mass appeared on the left side of the scalp, in the neighborhood of the scar of the previous operation. The clinical features of this mass were closely similar to those of the tumor extirpated in 1928. A steady extension of the growth was noted, so that by early in the year 1936 the

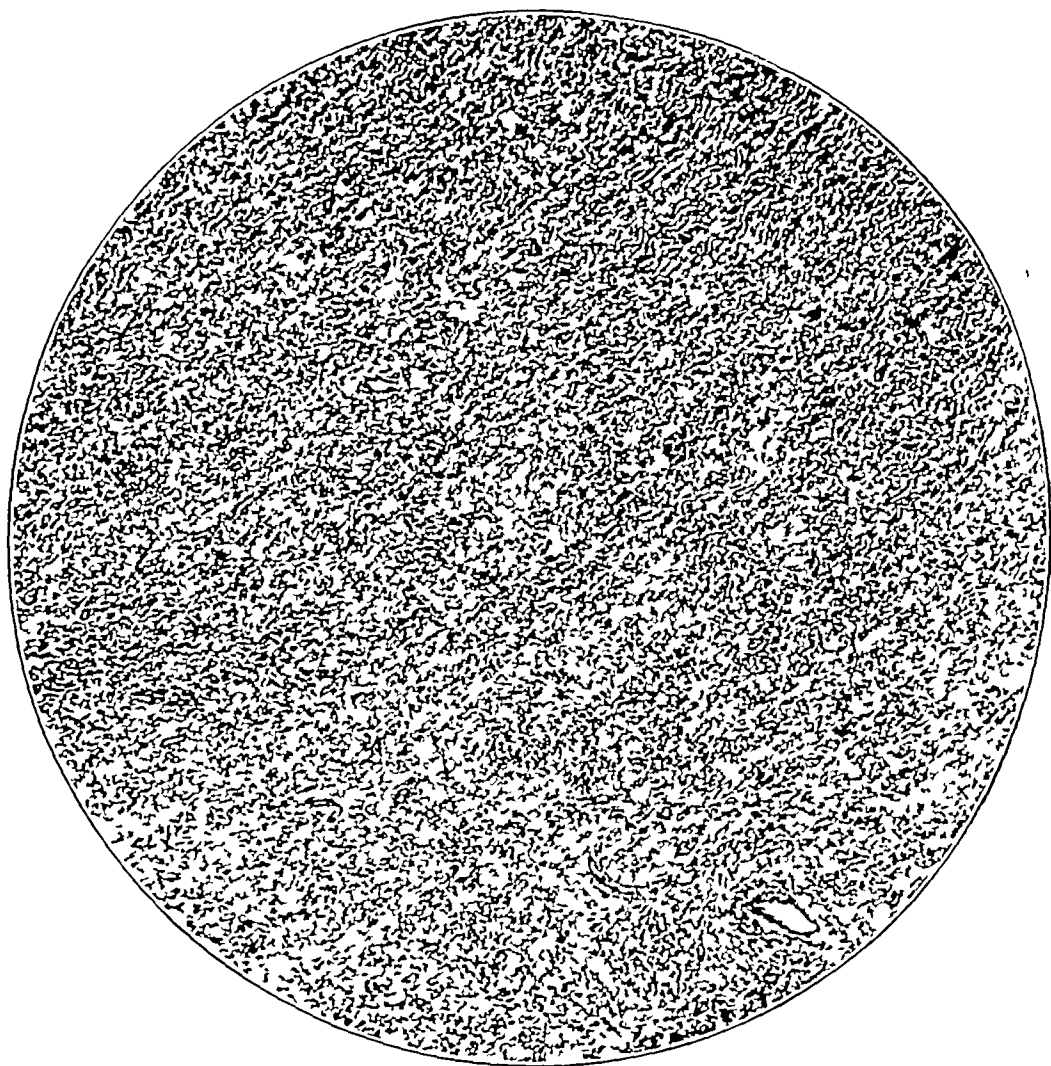


Fig 1—Photomicrograph (hematoxylin and eosin,  $\times 90$ ) of a specimen of scalp obtained at the time of the first operation (September 1928). The section shows young fibrous tissue with abundant fibroblastic cells and relatively poorly developed fibrils of the collagenous type. The blood vessels are few, and their walls, especially the muscularis, are poorly formed. Degenerative features are absent.

scalp overlying the entire left side of the vault became thickened and redundant, hanging in heavy, loose folds. The adjacent tissues of the upper part of the left side of the neck were similarly implicated by the growth. Between 1935 and 1938 there supervened hypertrophy of the left pinna and progressive sagging of the external ear. During this period the active growth of the scalp somewhat

slackened. Tenderness, pain and a tendency to ulceration were conspicuously absent throughout the history. From 1933 to 1935 the patient was treated for a discharge from the left ear. The records do not indicate whether it was clearly established that this discharge resulted from chronic otitis media. The skin of the external canal was described as eczematous. Boric acid douches were employed, and the discharge entirely subsided after two and one half years. Up to the present there has been no recurrence of this condition. At the time of his coming to the dispensary of the Kings County Hospital, in the fall of 1938, the patient's greatest concern was with the social embarrassments arising in relation to his appearance.

Physical examination disclosed the patient to be fairly well developed, affable and intelligent, with a striking asymmetry of the facies (fig 2). The scalp hung in loose folds from the left side of the head. The left ear was generally enlarged and thickened to approximately one-third again the size of its fellow. The skin of the external meatus was so thickened that the canal was all but occluded. The subcutaneous tissues of the posterior aspect of the left pinna were much hypertrophied and caused the ear to stand out prominently from the head. In addition, the pinna was displaced downward onto the neck so that its uppermost rim was visibly below the level of the tragus of the right ear. Palpation demonstrated that the redundant portion of the scalp varied in thickness between two and four times that of the normal (right) side. The cutaneous surface was soft and smooth, and the growth of hair was somewhat less vigorous over the redundant portion of the scalp than elsewhere. When the tissue was rolled between the finger tips it felt irregular, gristly and much like a bag of worms. Altogether, the cutaneous lesion implicated the posterior frontal, temporal, parietal and occipital regions of the left side of the scalp and the uppermost portions of the posterior triangle of the neck. A vertical scar 1 inch (2.5 cm) in length was visible over the left posterior parietal region. Beneath this could be palpated a bony defect roughly circular in outline and equal in area to a 25 cent piece. Within this defect a pulsatile sensation corresponding to the circulatory impulses of the underlying brain could be felt. There were rotatory kyphoscoliosis of the thoracic and lumbar levels of the spine and a corresponding deformity of the thoracic basket. The scar of the spinal fusion operation was well healed. General physical examination otherwise gave negative results. There were no positive neurologic findings. The temperature, pulse rate and respirations were normal, and the blood pressure in millimeters of mercury was recorded as 124 systolic and 100 diastolic.

Urinalysis revealed no albumin, dextrose or significant microscopic abnormalities. The hemoglobin content of the blood was 90 per cent (Sahli), and the red blood cells numbered 5,600,000 per cubic millimeter. There were 8,700 white blood cells per cubic millimeter, of which 68 per cent were polymorphonuclear leukocytes and 32 per cent lymphocytes. The value for blood urea was 39 mg, that for creatinine 1.26 mg and that for sugar 106 mg per hundred cubic centimeters. Examination of the serum revealed the value for calcium to be 11 mg and that for combined cholesterol 133 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Roentgenograms of the skull revealed nothing unusual except for the bony defect of the left parieto-occipital region resulting from the operation in 1928. This was slightly greater than 1 inch (2.5 cm) in diameter. The lung fields were clear.

Operation was carried out on Dec. 1, 1935, with the region under local procaine hydrochloride anesthesia. The essential steps of the procedure are illustrated in figure 3. A strip of fascia lata measuring approximately 7.5 by 4½ inches (22 by

11.3 cm) was first obtained from the right thigh. A large circumlinear cutaneous incision was then made in the left side of the scalp, beginning anteriorly at the temporo-frontal region and sweeping up to the vertex and backward to a point just lateral to the external occipital protuberance. This was carried deep to the bone. A second and lower incision, roughly corresponding to this, was

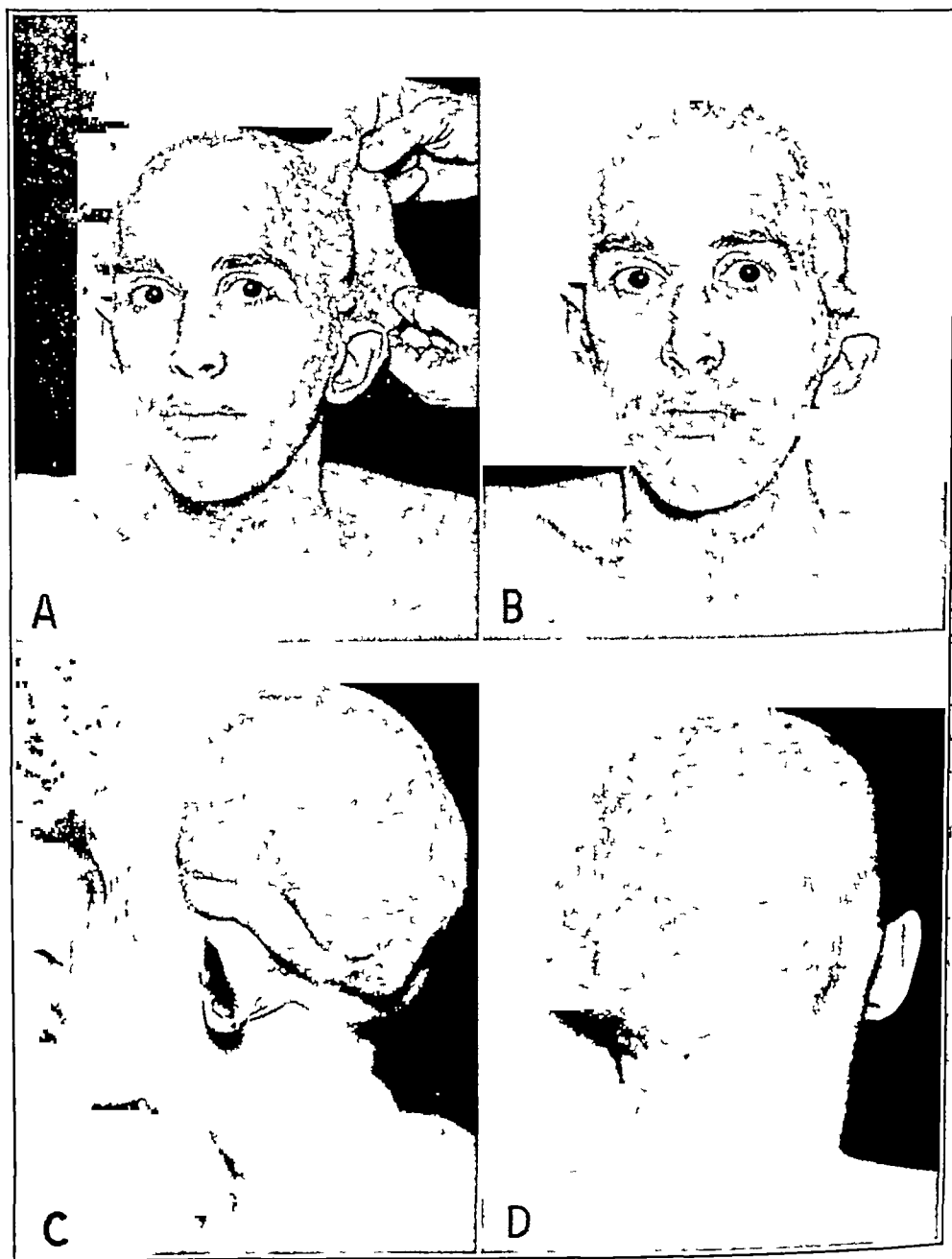


FIG 2—Preoperative photographs illustrating the thickening and redundancy of the left side of the scalp and the downward displacement and forward turning of the left pinna. In the lateral (C) and posterior (D) views the healed scar resulting from the operative procedure in 1928 is clearly visible.



fashioned so as to remove the redundant portion of scalp. A third incision in the scalp was made just above and behind the left pinna (fig 3 *A*). The postauricular tissues were undermined, and a dense mass of vascularized white fibrotic overgrowth was excised. The skin of the posterior portion of the pinna was reflected. The strip of fascia lata was now split lengthwise for one-third of its extent, and the two tongues so fashioned were sutured to the fascia and cartilage of the pinna, one anteriorly and the other posteriorly. The free end of the fascial strip was now burrowed under the scalp, and sufficient traction was exerted on it to bring the pinna up to a more nearly normal level (fig 3 *B*). Two small holes were drilled through the outer table of the skull, and the fascia was then secured in its new position by threading fine steel wire through the holes. In addition, a number of black silk sutures were employed to bind the fascial strip to the external fascia of the temporal muscle (fig 3 *C*). The scalp was closed in separate

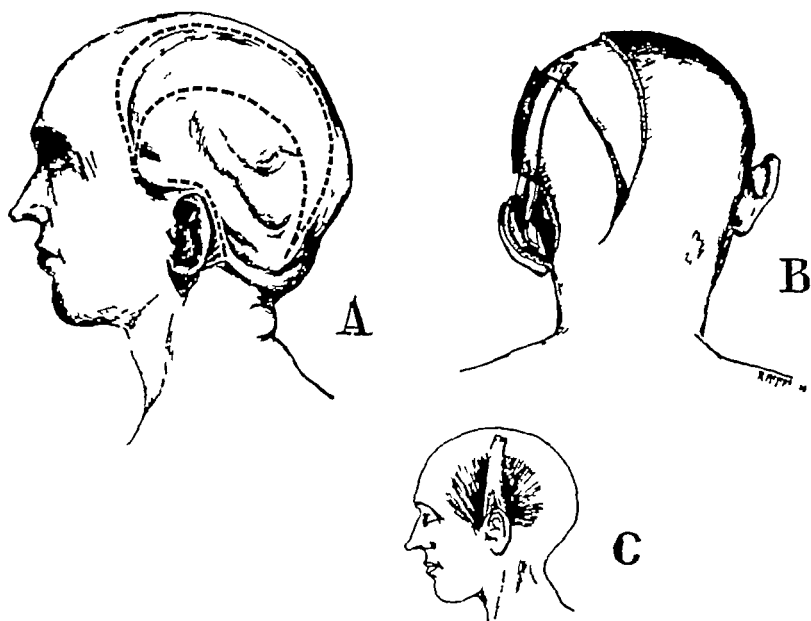


Fig 3—Operative procedure. The sketch at *A* indicates by broken lines the course of the scalp incisions. At *B* are illustrated the reflection of the skin from the posterior face of the pinna and the sites at which the two tongues of split fascia lata were sutured to the pinna. The free end of the fascial strip is shown beneath the scalp, secured to the vertex of the skull by steel wire sutures. At *C* are indicated black silk sutures binding the fascial strip to the external fascia of the temporal muscle.

layers, interrupted black silk sutures being used through the galea and skin. Five steel wire retention sutures were placed at regular intervals along the horseshoe-shaped incision. In anticipation of a serous or bloody ooze a Penrose drain was led from under the superior margin of the scalp flap out through the incision in the postauricular region.

The gross specimens consisted of several large crescent-shaped strips of scalp varying from two to four times normal thickness. The outer surface of the skin appeared healthy. The galea was thin but otherwise normal in appearance. The

cut section revealed a dense, white, irregular pearly-appearing tissue which occupied the position normally represented by the areolar layer. Microscopically, this consisted of large bundles of fibrous tissue in which were arranged many mesodermal cellular elements in parallel formation. The cells varied in shape from fusiform fibroblasts to more primitive stellate mesenchymatous cells. In the low power magnification numerous whorl-like patterns were prominent. The fibrous bundles were solely of the collagenous type. No elastic fibers were seen,

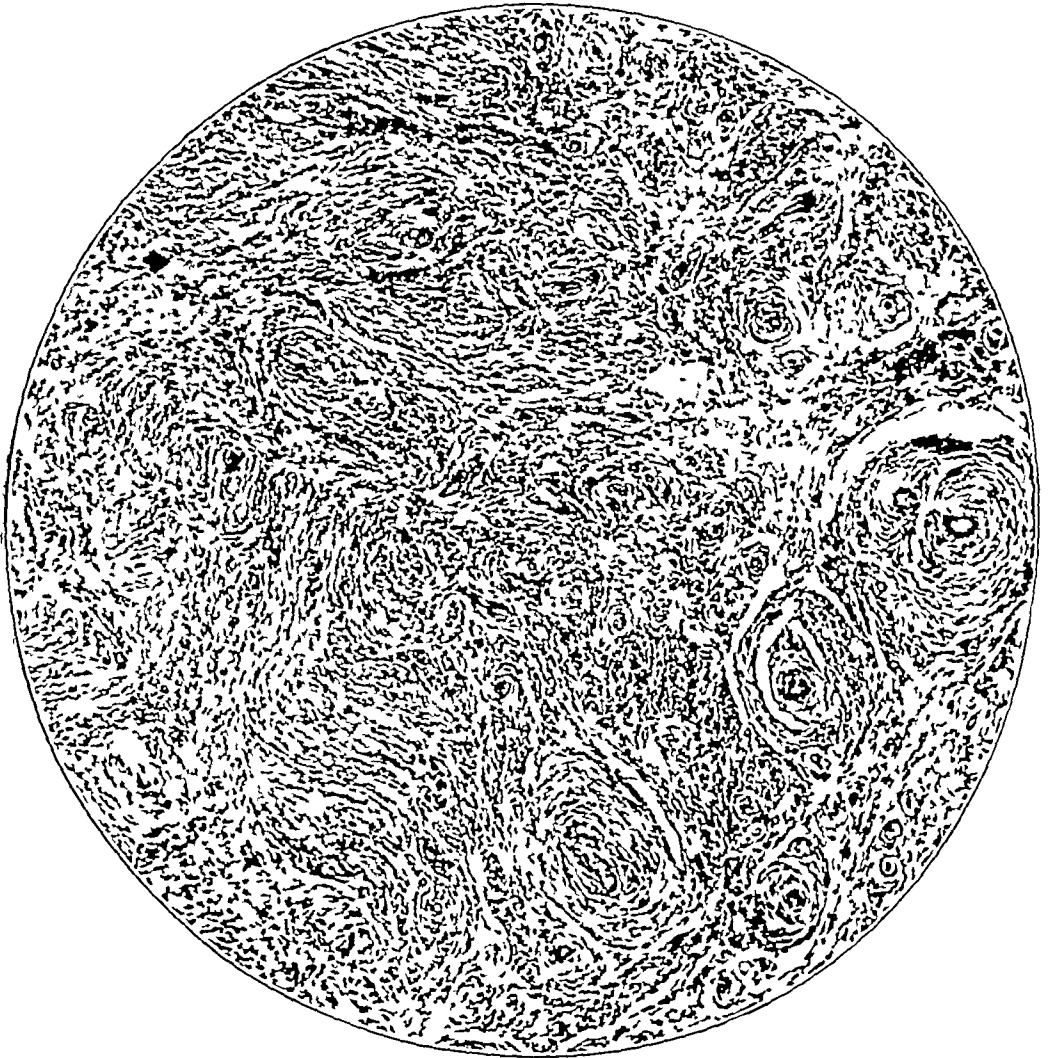


Fig 4—Photomicrograph (hematoxylin and eosin stain,  $\times 90$ ) of a specimen of scalp obtained at operation in December 1938. The general pattern is characterized by sheaflike bundles and whorls of connective tissue. The usual features of malignancy are absent. Fibroblastic elements predominate, ranging in type from spindle-shaped cells associated with much fibrous tissue to stellate mesenchymatous elements associated with a myxomatous matrix. Blood vessels are sparse and appear usually at the center of a whorl.

nor were there any epithelial elements. Between the adjacent capsules were scattered occasional round cells and plasma cells. In places, relatively clear blue areas representing a matrix of mucinous (myxomatoid) substance were visible (fig 4). In certain sections ringed-out nerve fibrils and aberrant ganglionic



Fig 5—Photomicrograph (hematoxylin and eosin,  $\times 50$ ), showing the large nerve nodules which lent to the tumor its plexiform character



Fig. 6—Photomicrograph (Weigert stain  $\times 50$ ), demonstrating the modified nerve tissue in the center of which there remain a few myelinated fibers. Marked proliferation of endoneurium and perineurium is visible within a loose connective tissue matrix.

cells were demonstrable within knots of dense connective tissue (fig 5) This feature appears to justify interpretation of the tissue as belonging to the complex tumors of the neurofibromatous group



Fig 7—Photographs taken two months after operation. The elevated position of the left pinna is demonstrated. Its hypertrophy is apparent. The lines of the healed incisions in the scalp may be made out. The vigor of growth of the hair in the normal portion of the scalp may be compared with that in the affected area.

The postoperative course was fairly satisfactory. The Penrose drain was withdrawn on the fourth postoperative day. At this time the skin sutures were

also removed. The large circumlinear incision healed by first intention. The ears matched well in respect to their position on the head. Toward the end of the first week a serous discharge appeared in the region of the postauricular incision, and within a few days the edges of the skin here revealed an undue redness, so that it seemed indicated to open the more anterior portion of the postauricular incision. No definite pus was encountered, and the wound remained clean save for a mild saprophytic invasion. Wet dressings were applied, and healing by second intention was achieved during the next three weeks. By the middle of



Fig. 8—Lateral view taken nine months after operation. No visible redundancy of the scalp is apparent, and the ear is maintained approximately in the normal position.

December the hair was growing over the scalp and the patient was discharged cosmetically improved (fig. 7). Close contact has been maintained with the patient since his discharge and there have been no significant alterations in the plastic result during the ten months since operation. The most recent photograph (fig. 8) was made on Sept. 1, 1939. Palpation at present fails to disclose any increase in thickness of the scalp tissues, and the skin everywhere appears to be applied closely to the vault. The upper margin of the pinna remains at approximately the same level as that noted immediately after operation.

## COMMENT

The present case represents a special type of so-called turban tumor. The generic significance of this term is of dubious value. Ronchese<sup>1</sup> attempted to limit its meaning to "nodular basal cell epithelioma of the scalp with cylindromatous degeneration." Other writers, however, have not conformed closely to this recommendation, the result of which is that the term connotes not a specific entity but merely a gross descriptive aspect of certain tumors of the scalp.

Although diffuse fibromatous tumors of the skin of the thighs, arms, trunk and buttocks (elephantoid tumors) are not uncommon, a careful inquiry into the literature of the past decade has failed to disclose a single recorded instance of tumor of the scalp which bears a close resemblance to that reported here. A number of standard works on plastic surgery, including those of Hunt<sup>2</sup> and Gillies,<sup>3</sup> have been consulted, but among these no comparable case is discoverable. MacCallum<sup>4</sup> described a case in which the histopathologic picture was similar but the clinical features were unlike those of the present case in that the tumor was rigid and formed a thick cap over the entire scalp. No mention was made of implication of the pinna by the growth. The only other recorded instance which even superficially resembles the present one was a case of mesenchymoma reported by Tauber, Goldmann and Barrett.<sup>5</sup> However, a tendency to ulceration and certain clearcut clinical and histologic evidences of malignancy permit a ready distinction between their case and that here reported. In his discussion of neurofibromatosis, Kaufmann<sup>6</sup> alludes to a case of elephantie plexiform neuroma in a girl aged 19. The clinical description, although meager, appears to resemble that of the present patient, and the microscopic pictures in the two cases are similar. In Kaufmann's case, however, the tumor was described as "growing rapidly toward the end."

Comparison of the histologic features of the specimen obtained in 1928 with that obtained in 1938 impresses one with the greater evidence of degeneration in the latter, viz., the more heterogeneous character of the fibrous matrix, the variability of cell types, the whorls and eddies

1 Ronchese, F. Multiple Benign Epithelioma of the Scalp (Turban Tumors), *Am J Cancer* **18** 875, 1933.

2 Hunt, H. L. Plastic Surgery of the Head, Face and Neck, Philadelphia, Lea & Febiger, 1926.

3 Gillies, H. D. Plastic Surgery, London, Oxford University Press, 1920.

4 MacCallum, W. G. A Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 948.

5 Tauber, E. B., Goldmann, L., and Barrett, C. Mesenchymoma. A New Type of Turban Tumor, *Arch Dermat & Syph* **37** 444 (March) 1938.

6 Kaufmann, E. Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 2025.

and the myxomatoid areas. Generally speaking, the ratio of fibrous to cellular elements is greater in the later specimen. It thus appears more "played out" than the early, more cellular fibroma. Observation of the patient during the ten months since operation affords some ground for the belief that the active growth of the scalp tumor may have reached a standstill. *This circumstance may have obtained for some time prior to operation.* Spontaneous cessation of growth is not, of course, an unusual feature of the life history of certain benign fibromatous tumors, the most notable illustration of which is provided by the common warts and pedunculated fibromas of the skin. Kaufmann<sup>6</sup> recorded the pertinent observation with reference to neurofibromatous tumors that "later the elephantiasis may become stationary." If this supposition should prove correct in the present case, the ultimate prognosis would be considerably improved in so far as the necessity for future surgical treatment is concerned.

The reason for such a "spontaneous" arrest of growth is not obvious, and it seems likely that the proper explanation will not be forthcoming until the present obscure understanding of the biology of normal growth and neoplastic processes has been clarified. The present paper is not the place for a detailed consideration of the problem, but the recent suggestion of Laidlaw<sup>7</sup> in this connection merits more than casual notice. This writer reconsidered the hypothesis of parasitic origin of certain neoplasms in the light of recent developments in virus research. He referred to the rather convincing experimental evidence of Rivers and Ward, Ledingham and Gye, Rous and Shope<sup>8</sup> that fibromas, sarcomas and myxomas can be regularly induced by the injection of viruses into animals of the avian and mammalian series. Not the least significant point of Laidlaw's discussion is the implication arising from the observation that antisera possessing power of agglutinating and neutralizing the "tumor agent" may be demonstrated. On such an immunologic basis it is conceivable that neoplastic growth might eventually be brought to a halt. The notion is highly stimulating because of its wide pathogenic and therapeutic significance, and it deserves further experimental inquiry.

Concerning the classification of the present specimen as a neurofibroma, it must be conceded that, in view of the incomplete state of knowledge this is somewhat arbitrary. It is by no means generally agreed that these tumors take their origin from neural elements. Some writers (Verocay, Durante) believe them to arise from Schwann sheath

<sup>7</sup> Laidlaw, P. P. *Virus Diseases and Viruses*, New York, The Macmillan Company, 1939, p. 36.

<sup>8</sup> Shope, R. E. *Infectious Fibroma of Rabbits. Infection with Virus Myxomatosis of Rabbits Recovered from Fibroma*. *J. Exper. Med.* **63**: 43, 1936.

cells Others (Wegelin) regard them as deriving from the endoneurial and perineurial connective tissues Still another view (Harbitz) holds that these tumors result from developmental anomalies of connective tissue and are akin in all basic respects to fibromas, myxofibromas and sarcomas Almost all writers agree with Durante and with Green and Bosanquet<sup>9</sup> that neurofibromas are prone to undergo metamorphoses, taking on the appearance of connective tissue, imbibing mucin and fat droplets and generally simulating the histologic characteristics of fibromas, myxomas and lipomas The common embryologic parentage (mesenchyme) of these several tissues seems to account reasonably for the demonstrable mutations

#### SUMMARY

An unusual instance of extensive plexiform neurofibromatosis of the scalp is reported The clinical history is supplemented by two histologic specimens, the first taken soon after the neoplastic process was established and the second a decade later, when, seemingly, further growth had been either arrested or markedly retarded The steps of the operative procedure employed to deal with the disfigurements incidental to the growth of the tumor are described In essence, they consisted of fascial suspension of the dependent pinna and extensive resection of the redundant portion of the scalp

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<sup>9</sup> Green, T H Pathology and Morbid Anatomy, revised and enlarged by W C Bosanquet, ed 10, Philadelphia, Lea Bros & Co, 1905, p 108



# LEIOMYOMA OF THE ROUND LIGAMENT

CHARLES W MAYO, M D

AND

GUSTAVE B SCHUNKE, M D

Fellow in Surgery, the Mayo Foundation

ROCHESTER, MINN

Wells<sup>1</sup> is generally credited with being the first to report a case of leiomyoma of the round ligament. In 1865 he reported 2 cases of inguinal tumors which were described as "fibrous tumors of the round ligament," one growth was the size of a small orange and the other the size of a coconut.

Sanger,<sup>2</sup> in 1883, found reports of 11 cases of tumor of the round ligament in the literature and added 1 of his own. In his case the tumor was a fibromyosarcoma. Emanuel,<sup>3</sup> in 1903, added 68 cases. Taussig,<sup>4</sup> in 1914, brought the total number of cases to 141.

Watkins,<sup>5</sup> in 1933, collected 173 cases of tumor of the round ligament from the literature, in 87 of these the tumor was a fibromyoma and was reported as a fibroma or a myoma. In 8 cases a diagnosis of sarcoma was made, and in all but 1 the sarcoma represented a malignant degeneration of a fibromyomatous growth.

Because of the inclusion of fibromas in the myomatous group, the exact number of leiomyomas which have been reported cannot be accurately ascertained. However, Horne,<sup>6</sup> in 1933, collected 36 cases of tumor of the round ligament which had been reported since publication of the article by Taussig in 1914. In 7 of these cases the tumor was a leiomyoma. In 1 case the growth was bilateral. Although a number of

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From the Division of Surgery, the Mayo Clinic

1 Wells, S. Fibrous Tumors of the Round Ligament of the Uterus, *Brit M J* **2** 484, 1865

2 Sanger, M. Weitere Beitrage zur Lehre von den primaren desmoiden Geschwulsten der Gebarmutterbander, besonders der Ligamenta rotunda, *Arch. f Gynak* **21** 279-308, 1883

3 Emanuel, R. Ueber Tumoren des Ligamentum rotundum uteri, *Ztschr f Geburtsh u. Gynak* **48** 383-427, 1903

4 Taussig, F J. Sarcoma of the Round Ligament of the Uterus, *Surg, Gynec & Obst* **19** 218-223 (Aug) 1914

5 Watkins R E. Tumors of the Fallopian Tubes, Ligaments, and Pelvic Cellular Tissues in Curtis, A H. *Obstetrics and Gynecology*, Philadelphia, W B Saunders Company, 1933, vol 2, chap 63, pp 1041-1088

6 Horne C F. Tumors of the Round Ligament, *Am J Obst & Gynec* **25** 446-448 (March) 1933

cases of tumors of the round ligament have been reported since 1933, the only case of leiomyoma was that reported by Pardini<sup>7</sup> in 1934

The largest leiomyomas have been those reported by Ward,<sup>8</sup> by Perewaloff<sup>9</sup> and by Craig<sup>10</sup> In Ward's case the tumor extended intra-abdominally, above the umbilicus, measured 46 by 48 cm and weighed 30 pounds (13.6 Kg) In Perewaloff's case the tumor was situated in the labium majus, it hung to the knees and weighed 31 pounds (14.1 Kg) However, the average diameter is usually given as approximately 5 cm

In Emanuel's series, the right round ligament was involved three to four times as frequently as the left Taussig, who after publication of Emanuel's report found 20 cases of tumor on the right side and 17 of tumor on the left side, doubted an actual preponderance for the right side In our series of 11 cases of leiomyoma only 4 of the tumors were on the right side

A leiomyoma may arise in any portion of the round ligament Watkins found that in 69 per cent of the reported cases of tumor of the round ligament the growth was extra-abdominal The fact that a superficial tumor is observed earlier and is more easily recognized than is a deep tumor may account for this greater frequency of extra-abdominal tumors of the round ligament Only 3 of the leiomyomas in our series were extra-abdominal (see accompanying table) A tumor which arises in the intra-abdominal, or peritoneal, portion of the ligament may become pedunculated or may grow between the leaves of the broad ligament One which arises near the internal inguinal ring may grow subperitoneally along the abdominal wall A tumor which originates within the inguinal canal may project through either inguinal ring, and has been known to grow upward between the muscles of the abdominal wall A growth which springs from the insertion of the round ligament in the labium majus appears as a tumor of the labium

Leiomyoma of the round ligament produces no characteristic symptoms A pedunculated tumor of the round ligament, like a similar tumor of the uterus, may become strangulated by torsion An intra-abdominal tumor of the round ligament usually is indistinguishable on physical examination from a uterine leiomyoma or an ovarian tumor One which is situated in the inguinal region or in the labia must be distinguished from hernia, from enlarged inguinal lymph nodes, from vari-

7 Pardini, I Un mioma della porzione intraddominale del ligamento rotondo, Clin ostet **36** 355-361 (June) 1934

8 Ward, W Large Fibroid of the Round Ligament, Am J Obst **77** 152, 1918

9 Perewaloff, cited by Craig<sup>10</sup>

10 Craig, R G Tumors of the Round Ligament, in Lewis, D Practice of Surgery, Hagerstown, Md, W F Prior Company, Inc, 1928, vol 11, chap 21, pp 1-8

*Clinical Data in Eleven Cases of Leiomyoma of the Round Ligament*

Case	Age years	Mar- ital State	Preg par- nets	Child- ren Born Alive	Symptoms	Site of Tumor			Size of Tumor	Associated Pelvic Disease	Clinical Diagnosis
						Round Lig- ament Involved	Portion of Ligament Involved				
1	43	M	1	1	Superficial abdominal tumor	Left	Inguinal		20 x 15 x 12 cm		Teratoma (?)
2	45	M	1	1	Occasional attacks of pain in right lower quadrant	Right	Intra abdominal		2 mm to 1.5 cm	Adenomyoma of right round ligament, multiple pedunculated leiomyomas of uterus	Cyst of right ovary fibroid uterus
3	32	M	1	1	None	Left	Intra abdominal		8 x 7 x 7 cm		Subperitoneal fibroid or tumor of ovary
4	45	M	1	1	Moderate urinary frequency soreness over bladder pain in left hip	Left	Intra abdominal		15 x 15 x 8 cm		Ovarian cyst
5	33	M	1	1	Dysmenorrhea abdominal mass	Right	Intra abdominal		7 cm		Uterine fibroid
6	42	S	0	0	Dysmenorrhea mass in right lower quadrant	Left	Intra abdominal			Leiomyomas of uterus	Multiple leiomyomas of uterus
7	35	D	0	0	Pain and lump in right lower quadrant lump became larger during menstrual periods	Left	Intra abdominal		7 mm to 4.5 cm	Pedunculated uterine leiomyomas chronic abscess	Endometriosis
8	40	M	4	3	Lump in right groin	Right	Inguinal				Omental hernia or cyst of round ligament
9	40	M	1	1	Dysmenorrhea pain in right flank and back	Left	Intra abdominal		2.5 cm	Leiomyoma of left fallopian tube purulent salpingitis on right side	Cyst of right ovary
10	37	M	1	0	Dull pain in right lower quadrant sensation of incomplete micturition	Left	Intra abdominal		2.5 cm	Multiple leiomyomas of uterus	Multiple leiomyomas of uterus
11	35	M	9	8	Mass in right labium	Right	Labial		6 cm		Cyst of labium

coclele, from hydrocele of the canal of Nuck and from other tumors of the round ligament, namely, adenomyoma (Neel<sup>11</sup>), fibroma, lipoma, dermoid and sarcoma. In the labia one must also rule out the Bartholin cyst and adenoma hidradenoides.

Attention was attracted to leiomyoma of the round ligament by one of us (Mayo), who recently operated in a case in which the patient had a tumor of the round ligament unusual in both situation and size. It was the largest leiomyoma of the round ligament that has been encountered at the Mayo Clinic. This case and the 10 other cases in which a tumor of the round ligament has been removed surgically at the clinic form the basis of this report.

#### REPORT OF CASES

**CASE 1**—A married woman aged 43 came to the clinic on May 3, 1939, because of a large superficial tumor on the lower part of the abdominal wall (fig 1). The patient had been pregnant only once, and the child had been born alive. There was no family history of diabetes mellitus, the patient's father had had hypertension.

Albuminuria had been present since the birth of her child, sixteen years before she came to the clinic, and she had had edema of the ankles for several years. She had always been obese. Five years before she came to the clinic she had noticed that "waves appeared before her eyes" when she did close work. Examination at that time had disclosed that the value for her systolic blood pressure was 200 mm of mercury. A diagnosis of hypertension had been made. Since then, her systolic blood pressure had varied between 160 and 180 mm. For a few weeks before she came to the clinic she had noticed that her vision for close work was worse than it had been previously.

In July 1935 she had noticed a mass about the size of a small lime in the left inguinal region. The mass had increased steadily in size and had extended toward the midline of the body. When the patient was first observed at the clinic the tumor was about 18 cm in diameter and hung down over the symphysis pubis. It had never caused any pain, and the only discomfort it had caused was the result of its size, weight and situation. The patient had received conflicting opinions regarding the advisability of surgical removal of the tumor.

The patient was 62 $\frac{1}{8}$  inches (157.8 cm) in height and weighed 193 pounds (87.5 Kg). The systolic blood pressure was 280 mm of mercury, and the diastolic pressure was 156 mm. The heart sounds, especially the aortic, were accentuated. The abdomen was large. A round mass about 18 cm in diameter was found in the lower part of the midline of the abdomen. The mass was attached to the left inguinal, labial and suprapubic regions by a broad pedicle. The mass did not transmit light. The uterus was of normal size. Examination also disclosed a cystocele, grade 2, and edema of the ankles, grade 1.

Examination of the ocular fundi disclosed narrowing, grade 1, and chronic hypertensive sclerosis, grade 1, of the retinal arteries. In a few scattered regions there were a postspastic type of uneven narrowing, grade 2, and small hemorrhages. There were a few "cotton-wool" exudates, which were undergoing absorption, and one large fresh exudate was found above the optic disk of the left eye.

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11 Neel, H. B. Adenomyoma of the Inguinal Region. Report of Three Cases, *Surgery* 2: 769-779 (Nov.) 1937.

Urinalysis disclosed albuminuria, grade 2, glycosuria (the concentration of sugar in the urine was 148 per cent) and a few hyaline and granular casts. Routine examination of the blood did not disclose any abnormality. Three hours after the patient had had breakfast the concentration of blood sugar was 240 mg per hundred cubic centimeters.

Roentgen examination of the thorax did not disclose any abnormality. An electrocardiogram revealed left ventricular preponderance and diphasic T waves in derivation I.

The clinical diagnosis was (1) a superficial tumor in the lower part of the abdomen (possibly a teratoma), (2) hypertension, grade 3, (3) obesity and (4) diabetes mellitus.

The diabetes was controlled by a dietary regimen. Operation was performed on May 8. Regional anesthesia was used to supplement the anesthesia produced

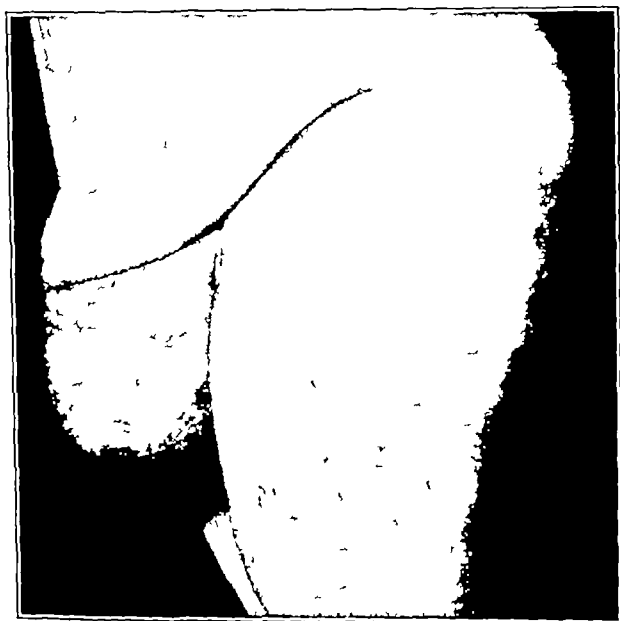


Fig 1 (case 1) —Tumor overhanging the symphysis pubis with a portion of its pedicle arising from the left inguinal region.

by the intravenous injection of pentothal sodium (sodium ethyl 1-methyl butyl thiobarbituric acid). An almost transverse elliptic incision was made across the tumor, which was well encapsulated and enveloped by superficial fascia. It seemed to be attached to the left round ligament and protruded through the left inguinal region as though it were a hernial sac. The peritoneal cavity was opened, and the round ligament was followed down to its uterine attachment. The tumor and adjacent portion of the round ligament were removed around the stump. The round ligament was brought to the pubic tubercle, the peritoneum was closed and the operation was completed as a left inguinal hernioplasty.

A cross section of the gross specimen had the typical appearance of a large leiomyoma which was undergoing degeneration in some places (fig 2). The pathologic report was as follows: Degenerating leiomyoma (fig 3), 20 by 15 by 12 cm, intimately attached to the left round ligament. Weight, 1,900 Gm."

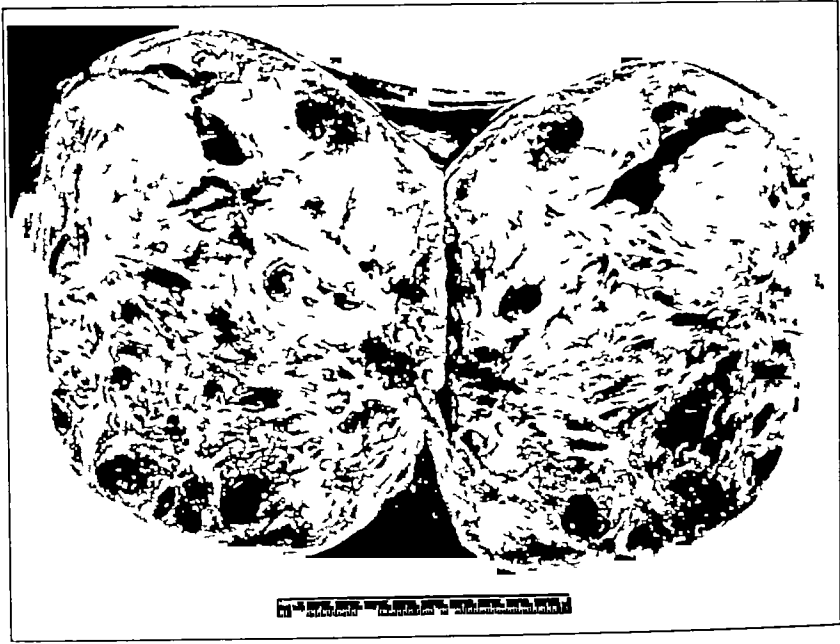


Fig 2—Cross section of the gross specimen in case 1

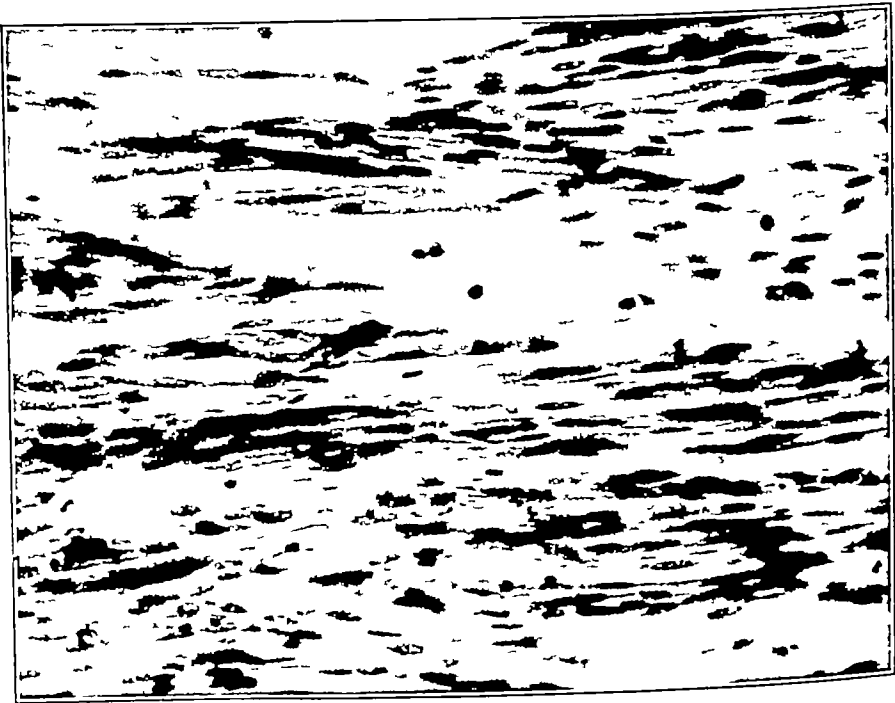


Fig 3—Photomicrograph of the tumor in case 1, showing smooth muscle, cells and edema,  $\times 185$

The patient made an uneventful recovery and was dismissed from the hospital in good condition on May 24. While she was confined to bed after the operation the systolic blood pressure was 175 mm and the diastolic pressure was 98 mm.

CASE 2—A married woman aged 45 complained of nervousness which had been present for many years and had been associated with occasional attacks of pain in the right lower quadrant of the abdomen. She had been pregnant only once and had given birth to a living child. Palpation revealed tenderness, grade 2, deep in the right lower quadrant of the abdomen. Pelvic examination disclosed what was thought to be a large cyst of the right ovary. A small nodule also was palpated above, and to the right of, the cervix. Operation disclosed multiple pedunculated uterine fibroids. The largest fibroid was 9 cm in diameter. An adenoma 3 cm in diameter was found in the right round ligament, about 5 cm from the uterus. Multiple leiomyomas also were present in the right round ligament. The diameter of the largest of these tumors was 15 cm, and that of the smallest was 2 mm.

CASE 3—A married woman aged 32 came to the clinic because of indigestion (which proved to be functional) and because of a pelvic tumor which never had caused any symptoms but had been discovered by her physician one week previously. She had been pregnant only once and had given birth to a living child. Pelvic examination disclosed a firm nodular tumor on the left side. It was thought to be a subperitoneal fibroid or an ovarian tumor. Operation disclosed that the tumor had arisen from the round ligament but was situated almost entirely within the broad ligament. A myomectomy with removal of a portion of the round ligament, 3 cm long, was performed. The tumor, which was a leiomyoma, measured 8 by 7 by 7 cm and weighed 120 Gm.

CASE 4—The patient was a married woman aged 48 who had been pregnant only once and had given birth to a living child. She came to the clinic because of moderate frequency of urination and soreness over the bladder, which had been present for nine months, and because of pain in the left hip, which had occurred occasionally during the previous two years. She was very obese, and her abdomen was pendulous. Palpation revealed slight tenderness over the bladder. Pelvic examination disclosed a soft, flabby cyst on the left side. The cyst reached almost to the umbilicus and was thought to be an ovarian cyst. Operation disclosed a cystic tumor which was attached to the left round ligament by a twisted pedicle. The tumor measured 15 by 15 by 8 cm and weighed 675 Gm. It was an edematous, subserous, pedunculated leiomyoma. Removal of the tumor relieved the symptoms.

CASE 5—The patient was a married woman aged 33 who had been pregnant only once and had given birth to a living child. She complained of menstrual pain situated in the lower part of the right side of the abdomen. The pain had occurred since puberty and had increased in severity. It had come on after the onset of the menstrual flow and had incapacitated her for three days each month. Her menstrual periods had been regular. Two years before she came to the clinic she had noticed a lump in the lower part of the abdomen. Pelvic examination at the clinic disclosed a tumor on the right side. The tumor was thought to be a uterine fibroid. Operation disclosed an intraligamentous leiomyoma which had arisen from the round ligament. The tumor was 7 cm in diameter, it was adherent to the right fallopian tube, the right ovary and the omentum. The right fallopian tube and the right ovary were removed with the tumor. The appendix also was removed. Since the operation, the dysmenorrhea has disappeared and the patient has given birth to two children.

CASE 6—A single woman aged 42 came to the clinic because she had noticed a mass in the right lower quadrant of the abdomen three weeks previously. Since puberty she had had menstrual pain in the right lower quadrant of the abdomen, and she had noticed some blood clots during her menstrual periods. "Gas pains" in the right lower quadrant of the abdomen had been present for eight years, and she occasionally had noticed spots of blood midway between her menstrual periods, which always had been regular. Abdominal and pelvic examination disclosed a large, hard, irregular tumor which filled the pelvis. The preoperative diagnosis was multiple leiomyoma of the uterus. Operation confirmed the diagnosis. The diameter of the individual tumors varied from 1.5 to 8 cm. The uterus, tubes and ovaries were removed. A myomectomy also was performed for a leiomyoma of the left round ligament. The size of this tumor was not mentioned.

CASE 7—A divorced woman aged 35 had never been able to become pregnant in seven years of married life. In 1924 an adenomyoma of the right round ligament and a draining sinus had been removed at the clinic. She had always had a slight pain in the right lower quadrant of the abdomen at the beginning of menstruation. In 1935 she came to the clinic complaining of severe pain which had been present in the right lower quadrant of the abdomen since the onset of menstruation, a week previously. She also had noted a lump in the right lower quadrant. This lump had enlarged during menstruation. On examination, motion of the cervix caused pain. The uterus was tipped to the right, and several small nodules were felt on it. It was thought that she probably had endometriosis. At operation, on Dec. 10, 1935, a congenital anomaly was found. There was no evidence of a fallopian tube on either side, and the only ovarian tissue found was situated high on the left lateral wall of the pelvis, extended downward and was incorporated in the round ligament, which was inserted in the wall of the uterus at a point about opposite the uterine artery. Along this ligament were situated three or four leiomyomas, which varied from 7 mm to 4.5 cm in diameter. A pedunculated fibroid was found in the left lateral wall of the uterus. The uterus and cecum were densely attached to a nodule in the right abdominal wall which proved to be a chronic abscess.

CASE 8—The patient was a married woman aged 49 who had been pregnant four times and had given birth to three living children. A month before she came to the clinic she accidentally had discovered a hard lump in her right groin. The lump had not caused any symptoms. The patient recently had missed two menstrual periods, but this was attributable to her age. Examination revealed an oval cystic mass on the right side of the mons. The mass could not be reduced. It was thought to be a right, indirect omental hernia or possibly a cyst of the round ligament or its coverings. Operation revealed a leiomyoma of the right round ligament.

CASE 9—The patient was a married woman aged 46. She had been pregnant only once but had not given birth to a living child. For three years before she came to the clinic she had had recurrent attacks of pressure-like pain in the right loin, flank and back. She also had had mild dysmenorrhea. Her menstrual periods were still regular, but the menstrual flow had become scanty during the six months before she came to the clinic. Pelvic examination revealed what was thought to be a cyst of the right ovary, which was the size of a peach. Operation disclosed a pedunculated leiomyoma of the left round ligament and a leiomyoma of the mid-portion of the left fallopian tube. The diameter of the tumor of the round ligament was 2.5 cm, and that of the tumor of the fallopian tube was 4 mm. Purulent salpingitis was present on the right side. The right tube measured 7 by 2 cm. Both of the tumors were excised and the right fallopian tube and right ovary were removed.



CASE 10—The patient was a married Negress aged 37, who had been pregnant once but had not given birth to a living child. A diagnosis of uterine tumor had been made two years before the patient came to the clinic. She recently had missed two menstrual periods, had had a dull pain in the right lower quadrant of the abdomen and had had a sensation of incomplete micturition. Palpation revealed a pelvic mass which extended upward as far as the umbilicus. The mass was thought to consist of uterine leiomyomas. A total hysterectomy was performed through the abdominal wall. The mass was found to consist of multiple intramural leiomyomas. The patient also had a leiomyoma of the left round ligament, this tumor was 2.5 cm in diameter.

CASE 11—The patient was a married woman aged 35 who had been pregnant nine times and had given birth to eight living children. A mass had developed in the right labium during the three years before she came to the clinic. It was thought to be a cyst of the labium. The mass, which was 6 cm in diameter, was excised. It was first reported to be a myxofibroma, but further study disclosed that it was a leiomyoma which probably had arisen from the round ligament.

#### SUMMARY

Leiomyoma of the round ligament has been encountered surgically at the clinic in 11 cases, in which the patients were women between the ages of 32 and 49 years. Ten of the women were married, 9 had been pregnant, and 7 had given birth to living children. The tumors varied in size from 2 mm in diameter to 20 by 12 by 15 cm. In 7 cases the growth was situated on the left side, and in 4 cases it was on the right side. In 2 cases it was multiple. In 8 cases the tumor was situated intra-abdominally in the peritoneal portion of the round ligament. In 2 of these cases the tumor was pedunculated, and in 2 other cases it was situated almost entirely within the broad ligament. In 3 cases the tumor was extra-abdominal, in 2 of these cases it was situated in the inguinal canal, and in the third case it was situated in the labium. A uterine leiomyoma was present in 4 cases. In 1 case there was also a myoma of the fallopian tube on the same side, and in another case multiple leiomyomas were associated with an adenomyoma of the round ligament.

In only 2 cases were there symptoms attributable to the tumor of the round ligament. Soreness of the bladder, frequency of urination and pain in the hip were present in 1 case, and severe dysmenorrhea was present in the other case. In both cases removal of the tumor was followed by disappearance of the symptoms. In 5 cases the symptoms were accounted for by other pelvic disease, and in 4 cases there were no symptoms aside from the presence of the tumor.

In none of these cases was the diagnosis made or suspected clinically. As has been stated, the diagnosis cannot be made if the tumor is intra-abdominal. However one should suspect a leiomyoma of the round ligament in any case in which a woman of the child-bearing age has a tumor which arises from the inguinal or labial region if the presence of a hernia or of other more easily recognized tumors has been excluded.

# ECTOPIC PREGNANCY

## ITS RELATION TO THE DIAGNOSTIC PROBLEMS OF THE GENERAL SURGEON

GUSTAV ZECHEL, M D

CHICAGO

The study of symptoms of ectopic pregnancy, augmented in this paper by observation of 81 patients treated surgically in the Ravenswood Hospital, Chicago, reveals results interesting not only to the gynecologist but to the surgeon, who faces the problem of differentiating "surgical" from "gynecologic" diseases of the lower part of the abdomen. Laboratory data which make the diagnosis almost specific, such as the Aschheim-Zondek reaction, are not always available, but once the possibility of an ectopic pregnancy is considered, these tests facilitate a more definite diagnosis. Although, as will be explained later, the blood counts are often bare of any diagnostic significance, there will be occasions when the patient's pallor and other manifestations of shock will make a diagnosis of internal hemorrhage definite. The only difficulty will be in determining the source of the hemorrhage, abnormalities in the menstrual history together with other manifestations, to be mentioned later, should lead one to the correct diagnosis.

### PROBLEMS OF PREOPERATIVE DIAGNOSIS

All authors who discuss the diagnosis of ectopic pregnancy agree that in many instances it is made with difficulty because of the variations in the symptoms which are known to be present in this disease. The clearcut examples, with the typical textbook manifestations, are easily recognizable. But the percentage of misdiagnoses is still too large. The physician who must make his decision from bedside examination only may often face a difficult problem, and in many cases the correct diagnosis is impossible because of the general and vague symptoms. When symptoms of a severe hemorrhage are unequivocal and there is time for an Aschheim-Zondek test, a definite diagnosis is obviously possible.

Scheffey, Morgan and Stimson<sup>1</sup> stated "Even today, the enigma of ectopic pregnancy confronts us as a diagnostic problem." The

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From the Ravenswood Hospital and the Departments of Anatomy and Surgery, University of Illinois College of Medicine

1 Scheffey, L. C., Morgan, T. R., and Stimson, C. M. An Analysis of a Series of Eighty-Two Cases of Ectopic Pregnancy, *Am J Obst & Gynec* 24: 103-115, 1932

correct diagnosis was made in 78.8 per cent of their cases before the operation

Urdan,<sup>2</sup> in his critical study of 474 cases, learned that the absolute diagnosis of ectopic pregnancy, except in the "tragic cases," is a difficult matter. The preoperative diagnosis was correct in 58.17 per cent of his series of cases.

Fitzgerald and Brewer<sup>3</sup> found 60.4 per cent of ectopic pregnancies correctly diagnosed, Jonas,<sup>4</sup> 73.3 per cent. These are percentages which have no bearing on the skill of the diagnostician but are an integral feature of the problem. A study of these reports also shows that there is a likelihood of diagnosing an ectopic pregnancy as some pathologic condition far removed from the pelvis.

Bubis<sup>5</sup> maintained that early diagnosis is difficult. He stated that "in many cases of typical textbook symptoms I found no extra-uterine pregnancy." Urdan stated, "The knowledge of ectopic pregnancy is complete but the diagnosis is still a difficult problem."

According to Jonas,<sup>4</sup> "A typical case of extra-uterine pregnancy is unmistakable, yet an atypical case, even after rupture, may deceive the most astute clinician." This author also admitted that the diagnosis is easiest when the symptoms are acute and that the general symptoms of pregnancy are often missing, his patients were admitted to the hospital as ill women and not as pregnant ones! Scheffey, Morgan and Stimson<sup>1</sup> found the concomitant signs of pregnancy infrequent. Fitzgerald and Brewer<sup>3</sup> maintained that because of the obscurity of the diagnosis, the patients not infrequently go to a medical or a surgical service. They observed that 10.2 per cent of patients were operated on with the definite diagnosis of an inflammatory disease, 10.6 per cent with a diagnosis of either ectopic pregnancy or an inflammatory process, and 4.6 per cent with an indefinite diagnosis of a "surgical" condition of the abdomen, this represents an error of 25.4 per cent.

Experiences of this character always maintain the surgeon's interest in the diagnosis of ectopic pregnancy, and this clinical entity, as such, remains within that professional area in which the surgeon's realm intrudes on the influential sphere of the gynecologist. Therefore, this paper is an attempt to scrutinize the diagnostic value of the symptoms.

2 Urdan, B. E. Ectopic Pregnancy, *Am J Obst & Gynec* **20** 355-372, 1930.

3 Fitzgerald, J. E. and Brewer, J. I. Extra-Uterine Pregnancy, *Am J Obst & Gynec* **30** 264-269, 1935.

4 Jonas, A. F., Jr. An Evaluation of Signs and Symptoms in the Diagnosis of Extra-Uterine Pregnancy, *New England J Med* **209** 1324-1328, 1933.

5 Bubis, J. L. Report on Seventy-Six Cases of Ectopic Gestation, *Am J Obst & Gynec* **17** 74-78, 1929.

which occur in ectopic pregnancy with particular reference to features which may lead to confusion with conditions in the field of general surgery

#### ONSET

The time at which ectopic pregnancy ceases to be only a pathologic entity and becomes also a clinical entity is usually characterized by the appearance of pain and a retrospective history of irregular menstrual bleeding. The early symptoms of ectopic pregnancy either are severe and sudden or develop gradually over a period of several days or weeks. The reports of the different authors agree closely in this respect. Sudden onset of symptoms, especially of pain, prevails in frequency over gradual development of discomfort. Falk and Rosenbloom<sup>6</sup> noted a sudden onset in 65.2 per cent, Jonas in 66.6 per cent and Fitzgerald and Brewer in nearly two thirds of all cases.

TABLE 1—*Ectopic Pregnancy*

	Number of Cases	Frequency in Percentage
1. Pain		
a. Sudden onset of severe pain in lower part of abdomen (indicating rupture of pregnant organ)	61	80.3
b. Gradually developing pain a long time before rupture (indicating the presence of a space-occupying process causing pressure)	12	15.8
c. No pain	3	3.9
Total	76	100.0
2. Fainting	13	16.0
3. Nausea and vomiting	29	35.8

#### SIGNS AND SYMPTOMS

In 80.3 per cent of cases (table 1) the patient was seized with sudden pain on one side of the lower part of the abdomen that caused a momentary disability. This pain indicates rupture of the pregnant organ and the peritoneal shock due to laceration of the peritoneal surface of the tube and consequent hemorrhage into the peritoneal cavity. Sudden symptoms, such as shock, collapse and unconsciousness, appear according to Bubis' experience, only when sudden massive hemorrhage occurs. In a smaller group of patients (15.8 per cent) the pain developed gradually, probably as a pressure symptom elicited by the space-consuming growth of the pregnant organ or by a slowly growing hematoma. Often the patient says she has had moderate pain and discomfort in the lower part of the abdomen for a number of days or weeks before the sudden

<sup>6</sup> Falk, H. C., and Rosenbloom, M. A. Extra-Uterine Pregnancy: Analysis of Three Hundred and Thirteen Cases from Harlem Hospital, Surg. Gynec. & Obst. 62: 228-235, 1936.

onset of severe pain In some patients the prodromal symptoms disappear for days Jonas found that severe pain with sudden onset is preceded by hours to weeks by inconstant colicky pain in the lower part of the abdomen According to this author, pain often loses its greatest intensity within half an hour, continuing less severely thereafter

*Pain*—This is the most common symptom of ectopic pregnancy, it is present according to Jonas in 97.7 per cent of cases and according to Fitzgerald and Brewer in 96.4 per cent My series presented a frequency of 96.1 per cent Curtis<sup>7</sup> explained the pain caused by rupture of a pregnant tube by tension of the peritoneum, its tearing and pressure of the extravasated blood on the peritoneum He accounted for the pain associated with tubal abortion by distention of the tube, muscular contractions of the tube and pressure of the extravasated blood In evaluation of pain as a diagnostic feature of ectopic pregnancy, three points must be considered the type, the localization and the course of its intensity

The pains as described by the patients with ectopic pregnancy may differ as may any other symptom of this disease They are usually characterized as sharp cramps, stabbing pains, bearing down pains, labor-like pains, dull pains, gas pains, backache, pain in the bladder or rectal tenesmus The latter two types of pain are noted particularly during micturition and defecation respectively Jonas observed 20 cases of vesical discomfort and 13 of rectal tenesmus

During the period preceding the rupture the pain is dull Sudden, stabbing pain is the sign of perforation of the tube

The site of the pain may vary greatly This fact is invaluable, because it may direct one's attention to an accurate diagnosis Therefore, a question pertaining to it should be asked the patient, since later the painful area increases in size and frequently comprises the whole lower half of the abdomen or more However, Fitzgerald and Brewer stated that in their series localization of pain was not of great help either in diagnosing extrauterine pregnancy or in determining its site Probably these authors had in mind the later spreading of the pain Tenney<sup>8</sup> observed pelvic tenderness in 92 per cent of cases Pain may occur all over the abdomen, in any of the four abdominal quadrants or only in the lower part of the abdomen It may also occur (though rarely) as an epigastric pain or a pain in the shoulder In a study of 474 cases Urdan<sup>9</sup> mentioned 28 patients who had pain in one or both shoulders Pain is therefore located most frequently in the lower part of the

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7 Curtis A. H. *Obstetrics and Gynecology* Philadelphia W. B. Saunders Company, 1933

8 Tenney B. *A Clinical and Pathological Study of One Hundred and Fifty Cases of Ectopic Pregnancy* New England J. Med. **214** 774-776 1936

abdomen The frequency reported by Tenney<sup>8</sup> was 93 per cent, that reported by Fitzgerald and Brewer,<sup>3</sup> 52.6 per cent

A confusing influence can be brought into the sometimes already complicated diagnostic picture by the change in severity of the pain At the time of rupture it begins primarily as a sharp, agonizing and disabling pain in the lower part of the abdomen, but, as has been said, it may disappear as quickly as it came and leave the patient with only a slight dull pain, which in many cases comes back hours or days later with changing intensity

*Fainting*—Attacks of fainting were present in 16 per cent of my cases This frequency comes close to that reported by some other authors Falk and Rosenbloom observed fainting in 18.8 per cent, Jonas, in 13.3 per cent Bubis encountered shock in 15.8 per cent, Scheffey, Morgan and Stimson, in 14.6 per cent The last-mentioned authors observed syncope in 26.7 per cent Fitzgerald and Brewer observed collapse in 18.2 per cent and fainting in 29 per cent of their cases, Urdan noted fainting in 28.91 per cent of his

*Nausea and Vomiting*—These symptoms were observed by Falk and Rosenbloom in 42.8 per cent and by Fitzgerald and Brewer in 37.4 per cent of cases In the Ravenswood Hospital series the percentage was 35.8 This frequency of nausea and vomiting is obviously an obstacle to strict differentiation of ectopic pregnancy from other abdominal diseases Scheffey, Morgan and Stimson observed this symptom in only 5 per cent of their cases, but they recorded it only when it was present at the time of admission to the hospital and omitted it from the statistics when it occurred at an earlier time

*Irregular Uterine Hemorrhage*—This is a frequent symptom It occurred in 73.5 per cent of the group studied by Falk and Rosenbloom Bubis noted it in 51 per cent, and Jonas' group reached the peak with 90 per cent In the total group described by the last-mentioned author, 60 per cent of the patients had missed one or more menstrual periods Scheffey, Morgan and Stimson counted 64.6 per cent of cases in which irregular bleeding occurred

Tenney classified cases of irregularity of the menstrual cycle associated with ectopic pregnancy into the following groups 45 per cent, one period missed, 52 per cent, one or more periods missed, 70 per cent, one or more periods missed or very scanty menstruation, and 82 per cent, irregular bleeding He stated that the absence of bleeding indicates a living embryo, with which rupture is more dangerous

Fitzgerald and Brewer reported the following data More than 33.3 per cent of patients did not miss a menstrual period, 11.4 per cent had bleeding which began as menstrual bleeding at a regular time but continued longer than a normal period, 12.8 per cent had the

normal period replaced by a diminished or intermittent flow ("spotting"), only 17.6 per cent had no bleeding during the ectopic pregnancy, 30 patients had symptoms before they missed a menstrual period, 58 patients missed periods but had no subsequent bleeding, 17.6 per cent had no bleeding between the time of the last period and the time at which the diagnosis was made, 50.6 per cent had only spotting following normal menses, 6.4 per cent had spotting for only one day, 20.6 per cent had moderate bleeding, and 8.2 per cent had profuse bleeding.

Urdan stressed the combination of irregular hemorrhage with pain in 89.83 per cent of his patients, because hemorrhage alone occurred only in 2.77 per cent of his cases and pain alone in 7.3 per cent. He also noted that the hemorrhages associated with ectopic pregnancy are of lesser intensity than those associated with threatened abortion.

TABLE 2—*Vaginal Hemorrhages in Ectopic Pregnancy*

	Number of Cases	Frequency in Percentage
1 Irregular hemorrhages of any kind during the interval between the last regular menstruation and the time of operation	48	70.6
2 At least 1 menstruation missed, but no irregular hemorrhage from the last menstruation to the time of operation	14	20.6
3 No regular menstruation missed before the operation and no irregular hemorrhage (i. e. before the next expected regular menstruation)	6	8.8
Total	68	100.0
Hemorrhage started with onset of pain	14	20.6

Falk and Rosenbloom observed irregular hemorrhages in 73.5 per cent of their cases, but in 14 per cent the acute symptoms began before the onset of the next expected regular period. Bubis recorded a 51 per cent incidence of irregular hemorrhages, Jonas found that 90 per cent of his patients had had vaginal bleeding at one time or another and that 60 per cent had missed one or two periods. In Scheffey, Morgan and Stimson's group the incidence was 64.6 per cent, Thiemeyer's<sup>9</sup> group had an incidence of 85.2 per cent of vaginal hemorrhages, and only 11.8 per cent of his patients had no vaginal bleeding.

In the Ravenswood Hospital series, irregular hemorrhages occurred in 70.6 per cent (table 2). They varied in duration and quantity from case to case. The cases could be grouped in gradual steps from those in which there were occasional vaginal hemorrhages up to those in which there occurred frequent, even daily, ones. In some cases the hemorrhages were described by the patients as slight spotting, in others, as profuse bleeding.

<sup>9</sup> Thiemeyer, A. C. The Diagnosis of Ectopic Pregnancy. M. Rec. 142: 373-375, 1935.

The cases in which there were no irregular hemorrhages amounted to 29.4 per cent. They can be divided into two groups. In the first (20.6 per cent) at least one menstrual period was missed, in the second (8.8 per cent), no regular menstruation was missed.

These statistical figures concerning the uterine hemorrhages associated with ectopic pregnancy indicate that in taking the history of a woman with abdominal symptoms special diligence should be exercised in discussing this subject in all its details with the patient, even though the tentative diagnosis may be acute appendicitis. One should also keep in mind that, in contrast to normal pregnancies, the overwhelming majority of ectopic pregnancies are associated with irregular hemorrhage.

The eliminated blood should be examined for particles of tissue. The presence of decidual particles with complete absence of fetal villi speaks for an ectopic pregnancy, the presence of both decidual particles and fetal villi, for the abortion of a uterine pregnancy.

*Blood Picture*—The diagnostic value of changes in the blood in cases of ectopic pregnancy depends on the amount of blood lost and the rate of hemorrhage above a certain minimum which is able to cause any significant change in the blood. From the standpoint of the surgeon, only a few important facts have to be kept in mind. Immediately after a hemorrhage there is no apprehensible change. Several hours are required after the loss of a certain amount of blood for replacement of the blood by body fluids, which causes dilution of the blood and hence a decrease in the red blood count. When no further hemorrhage takes place, the red blood corpuscles are replaced at the daily rate of about 50,000 to 80,000 per cubic millimeter. The hemoglobin content of the blood reaches its normal level much later than does the erythrocyte count. Within one or two hours after the hemorrhage, neutrophilic leukocytosis appears, in accordance with the general rule that leukocytosis follows hemorrhage in which the blood remains in a serous cavity, such as the peritoneal or pleural cavity, the subdural space or a joint cavity. Leukocytosis decreases at a rate comparable to the rate of absorption of the extravasated blood. Farrar<sup>10</sup> divided her 150 patients with ectopic pregnancy into three groups, with leukocyte counts of 4,500 to 10,000, 10,000 to 16,000 and 16,000 to 36,350 respectively. Of the first group, rupture occurred in 59.7 per cent. Of the third group, in which there was the highest leukocyte count, 100 per cent had either rupture or a tubal abortion. This study demonstrates that the white blood cell count fluctuates as a function of the phases of the hemorrhage.

It cannot be emphasized too strongly that changes in the blood picture occur after a relatively large loss of blood but that hemorrhage

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10 Farrar, L. K. P. The Value of the Leucocyte Count as an Aid to the Diagnosis in Ectopic Gestation, Surg., Gynec. & Obst. 41: 655-663, 1925.



below a certain minimum will not cause any appreciable change in the blood count. Therefore, in the presence of a normal blood count it is not justifiable to rule out ectopic pregnancy.

*Site of Ectopic Pregnancy*—One cannot escape the impression that ectopic pregnancy occurs more frequently on the right side than on the left, as may be seen from table 3, computed from the findings of other authors and confirmed also by my series. Only the series reported by Scheffey, Morgan and Stimson is an exception to this rule.

In the Ravenswood Hospital group it was found that 61.3 per cent (table 4) of the recorded cases were instances of ectopic pregnancy of

TABLE 3—*Sites of Ectopic Pregnancy Mentioned by Other Authors*

	Bubls <sup>5</sup>	Jonas <sup>4</sup>	Scheffey, Morgan and Stimson <sup>1</sup>	Thiemeyer <sup>9</sup>	Urdan <sup>2</sup>
Right tube	45	48	30	56	227
Left tube	31	26	43	48	187
Right ovary	2				
Left ovary	0				
Abdominal pregnancy	1				
Omental pregnancy	1				
Left tube (lithopedion)	1				
Site unknown	1				

TABLE 4—*Sites of Ectopic Pregnancy in the Ravenswood Hospital Series*

	Number of Cases	Frequency in Percentage
1. Right tube	49	61.3
2. Left tube	29	36.2
3. Ovary (left, 1 case; right, 1 case)	2	2.5
Total	80	100.0
4. Recurrent tubal pregnancy	4	5.0

the right tube. The left tube was the site of the ectopic pregnancy in only 36.2 per cent. Ovarian pregnancies had a frequency of 2.5 per cent. Ectopic pregnancy may occur more than once during the life of a patient, as can be seen from the 5 per cent of cases in which operation had been performed a second time for ectopic pregnancy. Jonas mentioned 2 cases (2.2 per cent) and Fitzgerald and Brewer 13 cases (2.6 per cent) of repeated ectopic pregnancy.

Bilateral ectopic pregnancy occurring simultaneously is an extremely rare finding. Johnson and Diasio<sup>11</sup> operated in 1 case of bilateral tubal pregnancy and collected 10 other cases from the literature.

<sup>11</sup> Johnson, H. H., and Diasio, I. S. Bilateral Tubal Pregnancy with Rupture of Both Tubes. *Am J Obst & Gynec* 17:116-117, 1929.

*Cullen's Sign*—Bluish discoloration of the umbilicus in the presence of free blood in the peritoneal cavity was not observed as frequently as one would expect. Bubis, one of the few authors who looked for this symptom, found it only in 3 of 76 cases. Jonas emphasized the fact that he had never observed this symptom.

*Type of Intra-Abdominal Hemorrhage*—It is of interest to add to this statistical study a summary of the different types of intra-abdominal hemorrhage found at the time of operation (table 5). The most frequent type was rupture of the tube into the free peritoneal cavity, the blood accumulating in variable amounts within the cavity (73.2 per cent). In 11.3 per cent of the recorded cases there was hemorrhage only from the fimbriated end of the tube with no rupture of the tube itself. The pregnant tube may rupture also into the broad ligament and form a hematoma in its loose connective tissue (2.8 per cent). Rupture of a pregnant ovary occurred in both instances of ovarian

TABLE 5—*Type of Intra-Abdominal Hemorrhage*

	Number of Cases	Frequency in Percentage
1 Rupture of tube and hemorrhage into peritoneal cavity	52	73.2
2 Hemorrhage from fimbria into peritoneal cavity	8	11.3
3 Not ruptured before operation	7	9.9
4 Rupture of tube and hemorrhage into broad ligament	2	2.8
5 Rupture of pregnant ovary	2	2.8
Total	71	100.0

pregnancy recorded in this paper, a frequency of 2.8 per cent of the total group of ectopic pregnancies.

The number of cases in which free blood was found in the peritoneal cavity is larger than that in which the tubes were perforated, because cases of tubal abortions and also cases in which there was an extravasation of blood into the tubal lumen, either by separation of the placenta or by erosion of a vessel, must be included.

Free blood in the peritoneal cavity was found by Scheffey, Morgan and Stimson in two thirds of all their cases.

The percentage of cases in which the diagnosis was made before the onset of acute symptoms and in which the pregnant tube was found still intact at the time of the operation was as high as 9.9.

*Local Physical Findings*—The value of the diagnostic aid obtained by inspection, external palpation and bimanual vaginal examination of the pelvic organs differs from case to case. The constitution of slender patients facilitates findings which, under equal conditions, cannot be made with obese patients.

Inspection of the abdomen of a patient suspected of having an ectopic pregnancy is of some diagnostic value with thin patients but of little or no value with obese patients. The intra-abdominal mass,

which consists of the enlarged tube and, after perforation, of extravasated blood and coagula, causes a slight bulging in the hypogastric region on the affected side, detectable by careful comparison with the normal side. Cullen's sign, for which one should search at the time of inspection, is present in only a small number of cases.

Palpation of the abdomen reveals a soft abdominal wall, except when peritoneal irritation is caused by a hematoma within the peritoneal cavity and by the pressure of coagula on the peritoneum (even then the muscular rigidity is by no means as intensive as with acute inflammations). However, the most careful palpation is apt to cause pain, often severe, in the region of the pregnant tube.

Bimanual vaginal examination makes it possible to outline a soft mass, often without any definite demarcation, in either lower quadrant. This examination should be performed gently, because of the imminent danger of hastening rupture of the friable wall of the tube or causing more hemorrhage from an already perforated tube. These two dangers and the pain caused by this examination limit considerably the scope of the method. Great thickness of the abdominal wall makes bimanual vaginal examination almost useless for the diagnosis of ectopic pregnancy. In many cases details cannot be made out, and the only result is the finding of a "diffuse mass", but under favorable circumstances the findings are practically specific. The uterus is soft and enlarged but far below the size to be expected with a normal pregnancy of the same term. The findings in the region of the parametrium, tube and ovary before rupture differ from those after rupture. The period before rupture can be considered the dormant period.

Before rupture, the mass, represented by the enlarged tube, is usually not large enough to be palpated with ease. The pain experienced by the patient when the enlarged part of the tube slips underneath the examiner's fingers is often of more diagnostic value than the information obtained by the examiner through his own sense of touch. This pain is often elicited by pressure applied to the cervix, or to the posterior vaginal fornix alone. In some cases the enlarged tube can be made out clearly by palpation, and its nature can be identified when it is possible to demonstrate its mobility.

After the rupture pain on palpation is occasionally diminished, unless a greater amount of extravasated blood accumulates, causing an irritation of the peritoneum. The pain at the time of perforation is intense and is often followed by collapse of the patient. The more or less circumscribed and fluctuating mass which is due to coagulation of the extravasated blood is distinctly palpable in a large majority of the cases, according to Behney.<sup>12</sup> It is noted in 85.5 per cent of all cases.

<sup>12</sup> Behney, C. A. Extra-Uterine Pregnancy. A Study of One Hundred and Sixty-Seven Consecutive Cases, J. A. M. A. 95 1557-1563 (Nov. 22) 1930.

## DIAGNOSIS

As has been indicated, ectopic pregnancy produces clinical manifestations before rupture of the tube which are different from those after rupture

(a) Before rupture of the pregnant tube the patient has a dull pain in one side of the hypogastric region. There are menstrual irregularities (either frequent, irregularly repeated uterine hemorrhages or complete absence of one or more menstrual periods). Abdominal distress, nausea or vomiting may occur, but never with such intensity as in the presence of acute inflammatory changes in the abdomen. Although the patient is able to go about and to perform her daily work, an enlarged uterus and a mass lateral to the uterus are palpable. The Aschheim-Zondek reaction is positive, but only in the presence of functioning chorionic tissue, after separation and death of placental tissue the reaction becomes again negative.

(b) After the rupture of the tube, most or all of the symptoms are intensified, and new ones aggravate the condition of the patient, who is in a state of shock associated with a crampy, severe pain in the lower part of the abdomen. Pain, dizziness and weakness force the patient to stay in bed. When the loss of blood reaches a certain amount, the patient appears anemic and the pulse is rapid and weak, the white blood count is elevated, but the red blood count is low. Severe pain is caused by palpation of the area of the pregnant tube. Irregularities of the menstrual history and a positive Aschheim-Zondek reaction make the diagnosis of ectopic pregnancy more definite, although, after perforation and death of placental tissue, the reaction will soon be negative. If the patient has any uterine hemorrhages at the time of examination, either before or after the perforation, the search for decidual shreds and chorionic villi is of great diagnostic help. The presence of decidual tissue is a definite proof of pregnancy, uterine or extrauterine, but its absence cannot be construed to the contrary. The presence of chorionic villi must undoubtedly be recognized as the most reliable sign of uterine pregnancy, and the diagnosis of ectopic pregnancy can be sustained only as long as no chorionic villi present themselves in the uterine discharge. In ectopic pregnancy the cervix becomes also soft and livid a short time after impregnation. Roentgen examination as an affirmative aid to diagnosis of ectopic pregnancy fails usually because the climax of the clinical progress is reached before the ossification centers of the embryo are demonstrable roentgenographically, which is possible not sooner than after the tenth or twelfth week of pregnancy.

It would be a mistake to explain the symptoms of secondary anemia only by the vaginal hemorrhage and not to take into consideration the possibility of intra-abdominal hemorrhage.

After perforation of the tube one can establish, according to the intensity of symptoms, two classes of condition (1) the urgent, or acute, and (2) the nonurgent, or "chronic" 1 With the former, all the symptoms are well pronounced, and some of them reach an alarming climax severe pain, prolonged collapse of the patient with slow recovery, anemic skin and mucous membranes, rapid and weak pulse, emptiness of the cutaneous veins, low blood pressure gradually falling in repeated readings, low red blood count and blood in the cul-de-sac, which is characterized by fluctuation in the posterior vaginal vault and is obtainable by paracentesis through the posterior vaginal fornix Therefore, pulse, blood count and blood pressure must be taken frequently and must be charted in order to help in evaluation of the progress 2 With the latter forms tubal rupture as a diagnostic problem is more puzzling than with the urgent conditions In the nonurgent conditions the internal hemorrhage is not so profuse as to produce any alarming symptoms of secondary anemia, repair to the point of recovery often takes place without surgical intervention, and during the period of repair some of the patients are able to pursue their daily routine Usually the only prominent symptoms are pain in the hypogastrium and vaginal hemorrhage, so that the condition is occasionally diagnosed as abortion or explained by some other erroneous diagnosis

#### DIFFERENTIAL DIAGNOSIS

The pain caused by ectopic pregnancy may not stay close to the region of its origin but may radiate to other areas of the abdomen and sometimes even to the shoulder, thus making the differential diagnosis a difficult problem A thorough history and a careful examination of the patient should disclose a pelvic origin for the pain Although the type of pain is sometimes pathognomonic, it may occasionally mislead the diagnostician because of its radiation throughout the abdomen The menstrual history must be discussed in detail with every woman who has abdominal symptoms Ectopic pregnancy should always be considered and eliminated before the diagnosis of any other abdominal disease is definitely made in the case of a woman of the child-bearing age The Aschheim-Zondek test should be performed whenever possible

*Normal Pregnancy*—Confusion of ectopic with normal pregnancy may occur when there is a uterus bicornis with the ovum implanted high up in one of the horns, in which case it is possible to palpate a spherical, well circumscribed and movable mass lateral to the midline Absence of pain, hemorrhage and other manifestations makes the diagnosis of ectopic pregnancy dubious

*Abortion*—Abortion is characterized by profuse hemorrhage during elimination of the fetal parts and crampy pains in the midline of the

hypogastrium which the patient herself recognizes as pains in the womb. The pain associated with abortion is intermittent, corresponding with the periodic contractions of the uterus. After the critical moment of elimination of the fetus under labor-like pains the patient feels relieved except for occasional cramps and hemorrhages, which may be profuse if elimination of the uterine contents is incomplete. The great amount of blood and its bright color when the uterus expels its contents are indicative of an abortion, an undramatic spotting or a scanty hemorrhage producing brownish "old" blood indicates, most probably, an ectopic pregnancy, provided that the other findings support this diagnosis. By inspection of the masses of blood clot, especially after they are carefully rinsed in water, some of the lumps can be identified as decidua or villi. The presence of villi always indicates abortion, whereas decidual shreds are present with ectopic pregnancy as well as with abortion. In some cases of abortion, the fetus and the placenta can be identified easily. In ectopic pregnancy the uterus is smaller than a pregnant uterus before its emptying.

*Rupture of an Ovarian Follicle*—This condition sometimes causes pains similar to those of ectopic pregnancy, but the other clinical symptoms are absent. Detailed inquiry regarding the menstrual history should be helpful, as repeated and regular occurrence of the same pain at intervals corresponding with the menstrual cycles is indicative of rupture of an ovarian follicle.

*Ovarian Cyst*—An ovarian cyst can obviously attain the same size as a pregnant tube. It is firmer, but it is also movable and may sometimes cause menstrual irregularities. There is no attack of severe pain except when the pedicle is twisted, the growth is not as rapid as that of a pregnant tube. During the few weeks' observation when the diagnosis of tubal pregnancy is being considered, the mass will remain unchanged in size if it is an ovarian cyst and a crisis typical of perforation of a tube fails to appear. It is not advisable, however, to confirm the diagnosis of ectopic pregnancy by waiting for spontaneous perforation. Furthermore, an ovarian cyst is usually larger when it first causes discomfort than a pregnant tube is even at the time of its rupture. The long duration of subjective symptoms, the large size of the tumor and the menstrual history should give the correct interpretation of the clinical picture. The significance of the menopause in this connection is self-evident.

An ovarian cyst with a twisted pedicle causes sudden pain and collapse of the patient as does rupture of a pregnant tube. The mass of the cyst is better outlined on bimanual examination than is the diffuse mass caused by the hematoma after tubal rupture. The fluctuation is palpable, indicates higher pressure in an ovarian cyst than in the mass

of the hematoma in ectopic pregnancy. An ovarian cyst will usually be palpable above the pelvic brim, which is a higher location than that attained by an ectopic pregnancy. Although leukocytosis may develop, there is no secondary anemia, and the pulse does not show the changes associated with ectopic pregnancy. The patient complains of distress in the lower part of the abdomen for a long time, sometimes for years, often stressing the occurrence of "indigestion" and uncomfortable sensations in the stomach.

*Salpingitis*—This condition does not cause a sudden attack as does perforation of a pregnant tube, but it may have in common with ectopic pregnancy the leukocytosis and menstrual irregularities. The pain of ectopic pregnancy, radiating sometimes across the midline, may simulate a bilateral hypogastric pain which is significant of salpingitis. Fever, a septic appearance of the patient, peritoneal symptoms and enlargement of the tubes causing a bilateral pelvic mass are present in cases of acute salpingitis. There is no anemia in the beginning of salpingitis, but it may develop in the later stages. The uterus remains normal in size and consistency. A history of gonorrhea or a purulent vaginal discharge and the occasional finding of gonococci in the discharge are typical of salpingitis.

*Uterine Fibroids*—When small, subserous and well demarcated from the uterus, or when intraligamentous, fibroids may sometimes give the same response to bimanual examination as an ectopic pregnancy. However, the fibroid is close to and movable with the uterus and is firmer than the pregnant tube. The history of the patient does not indicate pregnancy, and the physical signs of pregnancy are absent.

*Intestinal Obstruction*—Obstruction or strangulation of an intestinal loop located in one of the lower quadrants may also begin in a stormy manner, similarly to perforating ectopic pregnancy, but there is no history or sign of an existing pregnancy. The history of a previous laparotomy is important, since intestinal obstruction is commonly secondary to adhesions resulting from an operation. If the symptoms produced by the obstruction (whether secondary to adhesions or to carcinoma) are of more than a few weeks' duration, ectopic pregnancy is improbable. If the symptoms are produced by a malignant obstruction, there may be signs of failing health, such as loss of weight and anemia, such signs will of course be absent with ectopic pregnancy. The intestinal symptoms, such as vomiting, constipation, retention of gas and stool and abdominal distention, are more prevalent with intestinal obstruction than with ectopic pregnancy and take a more alarming course. With ectopic pregnancy visible peristalsis is absent. The typical pains and symptoms of internal hemorrhage occupy the foreground of the clinical picture of a perforated ectopic pregnancy. Palpation of the sites favored by hernia, i. e. inguinal, umbilical and femoral, may some-

times clarify the diagnosis by the discovery of a small strangulated hernia, which, owing to its small size, may escape detection by casual inspection

*Gallstone Colic*—This condition in a heavy-set patient of the child-bearing age with a short costinguinal distance and therefore a relatively low position of the gallbladder may arouse the suspicion of ectopic pregnancy but has nothing else in common with it except the severe pain

*Perforation of a Gastric Ulcer*—This occurs so rarely in women that its differentiation from ectopic pregnancy in the presence of symptoms of internal hemorrhage is seldom necessary

*Acute Appendicitis*—Acute appendicitis and perforated right tubal pregnancy have in common only the site of pain and the increased leukocyte count. Menstrual irregularities in a patient with a previously normal menstrual record are a strong indication of an ectopic pregnancy, and the finding of decidual particles is decisive proof of it. The onset of appendicitis is rarely characterized by sudden sharp pain and the collapse of the patient, both of which occur when the tube ruptures. Abdominal rigidity is more pronounced with appendicitis than with ectopic pregnancy. In appendicitis there is leukocytosis without anemia, but after rupture of the tube both leukocytosis and anemia are present. In cases of acute appendicitis the signs of pregnancy are absent, and no pelvic changes are found on bimanual examination. It must be borne in mind that in rare cases acute appendicitis may complicate an already existing pregnancy. The pain and tenderness of appendicitis are at McBurney's point, which is much higher than the area in which pain occurs with ectopic pregnancy. When the appendix is long and reaches down into the pelvis, the pains are localized correspondingly low and therefore can imitate those occurring in ectopic pregnancy. Vomiting, nausea and pain are predominant symptoms of appendicitis, though they do not occur in all cases. In cases of ectopic pregnancy associated with considerable hemorrhage the pulse is rapid and weak, whereas with appendicitis the pulse is rapid but of good volume.

Before rupture, pregnancy of the right tube must also be differentiated from so-called chronic appendicitis by evaluation of the menstrual history, the Aschheim-Zondek test, the location of the tenderness and other manifestations.

*Calculus*—A urinary calculus impacted in the lower part of the ureter causes pain in the hypogastrium, but the pain projects into the region of the external genitalia, and because of stagnation of urine in the ureter and in the renal pelvis the pain is also experienced in the renal region of the affected side. Such a stone may also cause pain in the bladder or stabbing pain in the rectum. Cystoscopic and roentgen examination and the search for occult hematuria will give complete information about the condition of the urinary system. The urine for



analysis must be obtained by catheterization, because in the presence of uterine hemorrhage the uterine blood may mix with the urine, which originally was free of blood. In reading the roentgen picture it must be borne in mind that because of the associated infection symptoms may persist for several days after the stone has passed.

#### SUMMARY

Ectopic pregnancy can be diagnosed without any difficulty when all the symptoms are clearly developed: irregularities of a previously normal menstrual cycle, typical pains, general symptoms of pregnancy and typical physical and laboratory findings. The menstrual irregularities consist either of complete cessation of the menses or of irregular hemorrhages. Particles of decidua can be detected in the discharge, chorionic villi are evidence against the presence of ectopic pregnancy. The constitutional changes in a patient with an ectopic pregnancy are the same as those observed with a normal pregnancy. The pain is located in one of the hypogastric regions, it is dull and lasts for a few weeks (the dormant period), until a sudden sharp pain sets in (at the time of spontaneous rupture of the tube), followed by shock and vomiting. The uterus is only slightly enlarged, and a mass is palpable in the adnexal region lateral to the uterus. The Aschheim-Zondek reaction is positive. These symptoms are observed during the dormant period of the ectopic pregnancy, *i. e.*, before perforation of the tube.

After perforation of the tube all these symptoms are overshadowed by shock, pain and symptoms of internal hemorrhage, with the typical changes in the pulse and blood picture. These symptoms can assume an alarming degree of intensity, endangering the life of the patient and thus constituting an emergency. On the other hand, there are instances in which the hemorrhage and shock are only moderate, in such cases the patient may recover without surgical intervention. In cases in which the hemorrhage is slight, it is obviously difficult to make a definite diagnosis of ectopic pregnancy. The patient does not appear dangerously ill but presents a clinical picture which makes it necessary to differentiate more carefully between ectopic pregnancy and other gynecologic and surgical diseases of the abdominal cavity.

The surgeon must always think of the possibility of ectopic pregnancy, unruptured or ruptured, when examining a patient of the child-bearing age with symptoms of an acute or a subacute process in the lower part of the abdomen because ectopic pregnancy in both of its stages shares many symptoms not only with gynecologic but with surgical diseases of the lower part of the abdomen. The diagnosis is difficult in many cases, as was explained in the introductory paragraphs of this article and it often happens that the patient is first seen not by the gynecologist but by the surgeon.

# CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS

HAROLD L STEWART, M D

Pathologist, United States Public Health Service

BETHESDA, MD

AND

M M LIEBER, M D

AND

D R MORGAN, M D

PHILADELPHIA

Carcinoma of the extrahepatic bile ducts is a rare condition. Text-books make few references to it, and the published reviews are fragmentary. Early diagnosis is essential, yet clinicians rarely consider it. The lesion may be found unexpectedly at laparotomy, and the surgeon is frequently at a loss as to the best methods of handling the situation. It is proposed to report 6 new cases of this condition and to correlate the data from these with those previously reported with a view to presenting a comprehensive picture of the morbid anatomic and clinical aspects of the disease.

Three earlier papers have been published dealing with cancer in closely related structures, namely, carcinoma of the suprapapillary portion of the duodenum (Stewart and Lieber), carcinoma of the intrapapillary portion of the duodenum (Lieber, Stewart and Lund) and carcinoma of the peripapillary portion of the duodenum (Lieber, Stewart and Lund).

## ANATOMY

The extrahepatic bile ducts present such frequent variations in length, course, structure and relation that it is difficult to draw a sharp line between normal and pathologic anatomy. Also, topographic variations are dependent in part on functional states of the extrahepatic biliary system and of regional structures, such as the liver, gallbladder, pancreas, stomach and duodenum.

The right and left hepatic ducts appear in the transverse fissure of the liver and unite at an angle of 80 to 90 degrees, forming the common hepatic duct, which extends downward, backward and mesially in the gastrohepatic ligament. The common hepatic duct varies in length

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From the United States Public Health Service, National Cancer Institute, and the Departments of Pathology and Neoplastic Diseases, Jefferson Medical College

from 1 to 10 cm, averaging about 3.5 cm, depending on the level at which it is joined by the cystic duct. The duct crosses the portal vein and branches of the hepatic artery, and, as it emerges from the hilus, it overlies the anterolateral aspect of the portal vein, the hepatic artery proper usually coursing to the left of the duct.

The cystic duct, a continuation of the neck of the gallbladder, varies from 0.5 to 6.5 cm in length, averaging 3 to 4 cm. The upper, easily movable, proximal portion has a redundant lining arranged in spiral folds to produce the valve of Heister. The lower, more fixed, distal portion of the duct is almost smooth and courses downward toward the left to join the hepatic duct. Pallin described high union, in which the confluence of the ducts lies 1 cm or more above the upper border of the duodenum, and low union, at the level of the upper border of the duodenum or beneath it. In about half the subjects examined by Pallin, the cystic duct ran parallel with the hepatic duct for a variable distance and united with it about the upper border of the duodenum. Nuboer, following the classification of Ruge, Eisendrath and others, described three types of union: (1) the angular type seen in 36 per cent of cases, usually on the right of the hepatic duct, (2) the parallel type seen in 36 per cent of cases, usually deep behind the duodenum, and (3) the spiral type, seen posteriorly to the left in 28 per cent of cases.

The common bile duct varies from 4 to 10 cm in length, averaging 6 to 7 cm, and is described in three parts. The suprapancreatic portion lies behind the duodenum and varies in length according to the point of confluence of the cystic and hepatic ducts. When this point of confluence is low the suprapancreatic portion is lacking. It descends along the right margin of the lesser omentum to the right of the hepatic artery, anterior to the portal vein. The pancreatic portion extends through a groove or tunnel in the posterior surface of the pancreas to its entrance into the descending duodenum. This segment is 3 to 5 cm in length and is separated from the vena cava by connective tissue alone or by a thin layer of pancreas. The duodenal portion extends obliquely through the wall of the duodenum. A detailed description of this portion is found in the recent study by Dardinski.

#### CARCINOMA OF THE HEPATIC DUCT

Three new cases of carcinoma of the hepatic duct are reported. Fifty-six cases were abstracted from the literature, 32 of which were regarded as acceptable on the basis of a clinical history and gross and microscopic studies of the primary neoplasm<sup>1</sup>. Six additional cases,

<sup>1</sup> Korczynski, Schüppel, Jenner (cases 1 and 2), Bezançon, Hesper, case 2, Chasse, Schuchardt, Schulze, Howald, Ingelrans, Porot, Rocco, Houssin.

probably authentic examples of this condition, were not utilized because of lack of a clinical history or because of insufficient data.<sup>2</sup> Eighteen cases were discarded because histologic studies were lacking in 15<sup>3</sup> and because of the possibility that the neoplasm may have been primary in the gallbladder in 2 and in the intrahepatic biliary ducts in another.<sup>4</sup> Thus there is a total of 35 cases of carcinoma of the hepatic bile ducts for analysis.

#### REPORT OF CASES

CASE 1—J. K., a white man aged 82, was admitted to the Philadelphia General Hospital on Nov. 13, 1935, with pain, jaundice, bloody expectoration, abdominal distention, dark urine and putty-like stools of two months' duration. The jaundice appeared suddenly and increased progressively, it was preceded by attacks of severe, sharp abdominal pain. This radiated from the back over the entire upper part of the abdomen. There were increasing weakness, loss of weight, anorexia and vomiting. Physical examination showed impaired resonance, bronchial breathing and subcrepitant rales in both lungs. There was gaseous distention of the abdomen, with slight dulness in the flanks but no signs of fluid. The liver and spleen were not palpable. The urine was dark amber and acid, with a specific gravity of 1.012, it contained albumin but no sugar. The clinical impression was that of carcinoma of the common bile duct with peritonitis and bronchopneumonia. The patient lapsed into coma and died on November 15.

Autopsy was performed eighteen hours after death. The combined gross and microscopic diagnoses were (1) scirrhous adenocarcinoma of the junction of the right and left hepatic ducts, with infiltration of the surrounding liver, (2) hydro-hepatosis and marked jaundice, (3) arteriosclerosis of the aorta and coronary arteries, with acute myocardial degeneration, (4) bronchiectasis of the left lung, (5) biliary nephrosis, and (6) acute fibrinous peritonitis.

The peritoneal cavity contained 2,000 cc. of bile-stained serofibrinous fluid.

The stomach and duodenum showed no visible change. The small intestine contained black material and dark red blood.

The liver weighed 1,200 Gm. and was flabby and deeply bile stained. The surface was mottled with deep green markings, and varicose ducts were present, especially along the margins. Soft, nodular elevations on the surface corresponded to dilated ducts beneath. The liver cut with slightly increased resistance, revealing loose, friable parenchyma deeply mottled with green, brown and yellow. The cut surface showed many dilated ducts, which contained pale, thick mucous fluid.

Lapointe, Raymond and Merle, Adlercreutz, Gutowitz, Petren, cases 14 and 16, Wahl, case 4, Wylegschann, McLaughlin, case 4, Bosco, Shapiro and Litvendahl, case 12, Milles and Koucky, David, cases 1 and 2, Lampert and McFetridge, Perez Fontana, Anastasia and Castro, case 1, Hess and Faltitschek, case 2, Walters and Olson, Leiter

2 Aufrecht, case 1, Netter, Jenner, case 3, Schmitt, case 3, Saltykow, case 7, Ikuta

3 Bristowe, von Plazer, case 2, Bressy, Debove, Stieda, case 4, McGlavin case 3895A, Petren, cases 9 and 13, Blomstrom, case 2, Ramlau-Hansen, case 6, Harnisch, case 1, Cabot, case 20331, Hess and Faltitschek, cases 1 and 5, La Manna, case 2

4 Willigk, Pittorino, Scudder and Richardson

Both main intrahepatic ducts were obstructed at a point just proximal to their convergence. Here there were constriction, marked thickening and angulation, and the lumens were narrow and slitlike. It was doubted that bile could have



Fig 1 (case 1)—Dissection of the hepatic ducts above and the common bile duct below. The dark probe is in the cystic duct and the papilla of Vater is at the extreme bottom of the illustration. Note the constrictions in the hepatic ducts above and the thickened, fissured, irregular mucous membrane.  $\times 1$

escaped spontaneously through these channels during life. The lining of the right, left and common hepatic ducts was thick, gray, fissured and granular (fig 1). The gray tissue on the surface extended through the wall of the duct and was continuous with a firm gray tumor nodule, 3 cm in diameter, embedded in the surrounding liver. Extensions of this tissue infiltrated along the large portal radicles for a short distance into the liver. The common bile duct below the lesion was neither thickened nor distended and emptied into an ampulla of Vater together with the duct of Wirsung, which also showed no visible change. The cystic duct

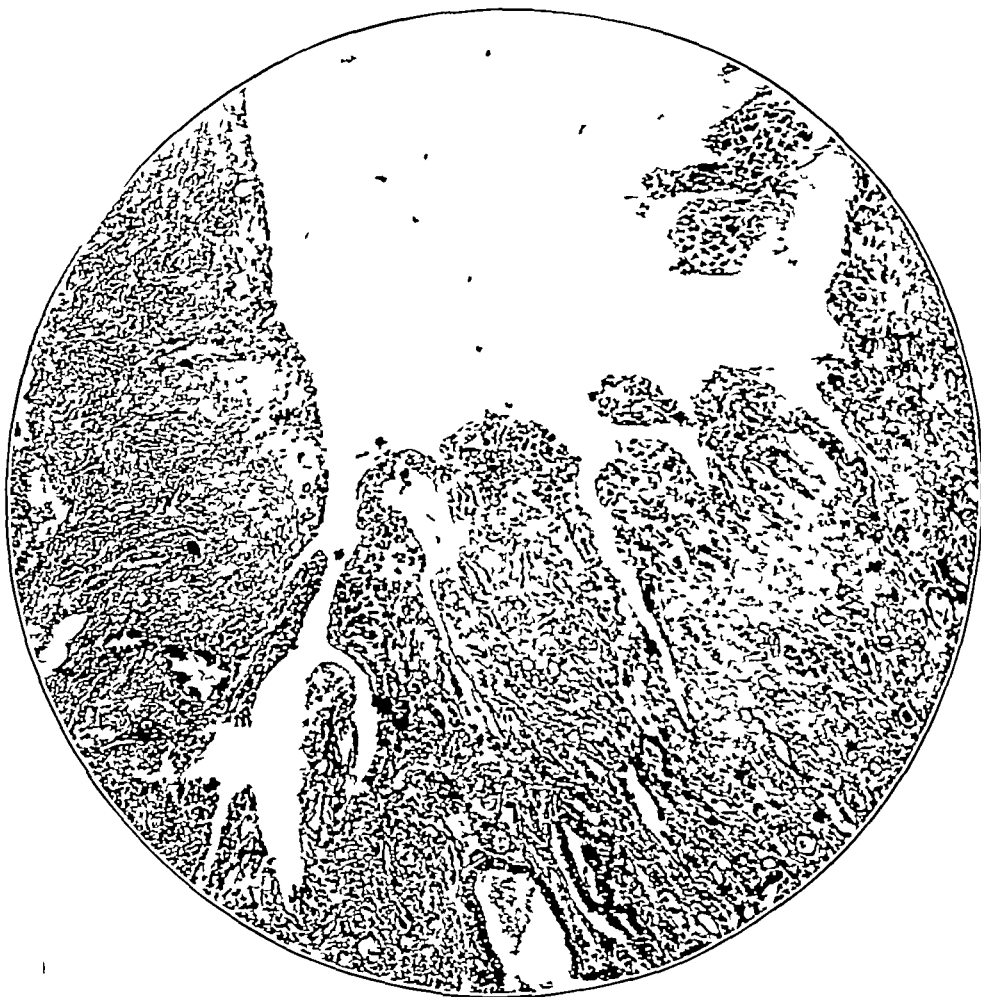


Fig 2 (case 1)—Hepatic duct, showing an area of malignant transformation near the deep fissure to the left. The first change is a slight piling up of atypical epithelial cells on the surface. Then, in succession, there are the formation of several long, narrow and broad papillary projections and an invasion of atypical epithelial cells through the duct wall into the surrounding tissue.  $\times 50$

opened into the common hepatic duct well below the point of obstruction. The gallbladder showed no visible abnormality, it contained 20 cc of pale, opalescent mucous fluid entirely devoid of bile pigment. The cystic duct was unobstructed.

Several sections through the common and right and left hepatic ducts were studied microscopically. In most of these the mucous surface and underlying wall

of the duct were invaded by atypical epithelial cells. In other sections only a segment of the duct was involved by neoplasm, and an area of malignant transformation was clearly evident on the surface (fig 2). The uninvolved duct was lined by thin, intact cells, the wall was slightly fibrotic and infiltrated with lymphocytes and monocytes, and the mural glands were slightly hyperplastic. The first significant change near the neoplastic margin was a piling up of cells on the surface, followed by formation of several long, papillary projections and extension of neoplastic cells through the wall of the duct into the surrounding tissue (figs 2

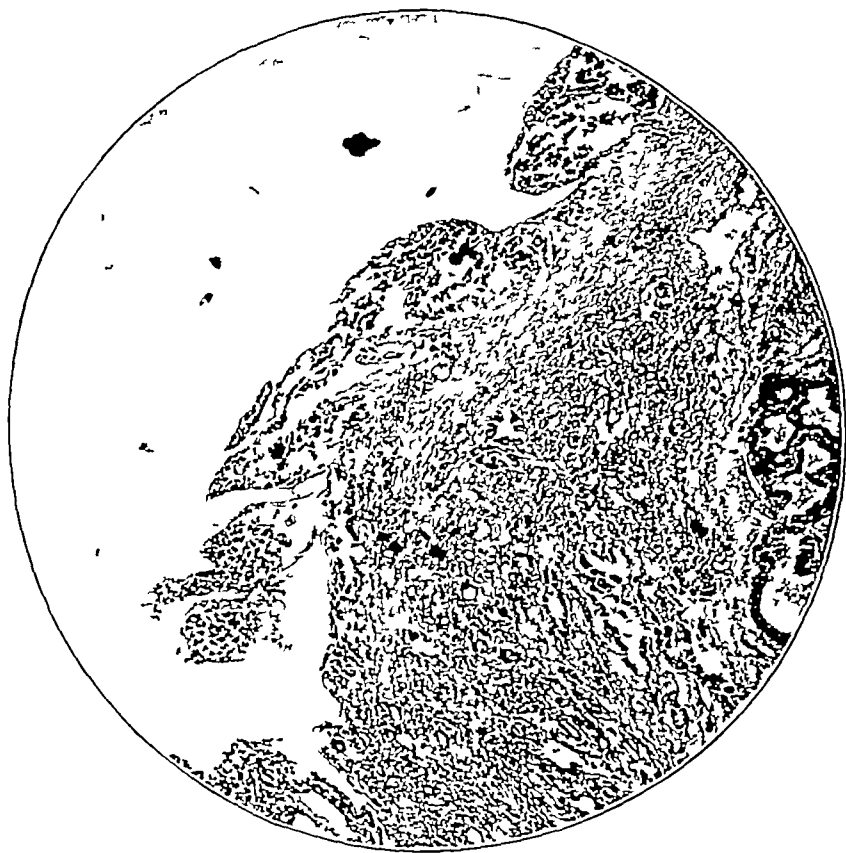


Fig 3 (case 1)—Hepatic duct, showing broad papillary neoplastic excrescences on the surface with permeation of the wall and underlying tissue by atypical epithelial cells which are frequently arranged as acini  $\times 50$

and 3). The surface of the duct was slightly ulcerated in places, and the arrangement of the connective tissue of the wall was distorted.

The neoplastic cells varied considerably in size and shape, from single nucleated elongated cells to large giant cells containing four or more nuclei or a single large multilobed nucleus. Intermediate forms were cuboidal and columnar. The nuclei usually stained uniformly, only a few showing hyperchromasia. Occasional mitotic figures were seen. The cytoplasm was pink, granular, homogeneous or finely

vacuolated and sometimes contained droplets of mucin. Groups of five to twenty tumor cells were arranged in the form of small acini. A few large acini showed papillary formations and contained debris and mucus in their lumens. Other tumor cells occurred in the form of strands, clumps or imperfect acini with perineural and perivascular infiltration. The stroma was abundant and slightly vascular.

CASE 2—E. C., a white man aged 52, was admitted to the Philadelphia General Hospital on Jan. 19, 1930. He had clay-colored stools, dark urine, jaundice, pruritis, gradually increasing weakness, loss of weight and dyspnea of four or five months' duration. Three days before admission to the hospital there was severe, intermittent abdominal pain accompanied by bloody stools. The abdomen was distended and tender. There was fulness in the flanks, and evidence of free abdominal fluid was noted. The liver was greatly enlarged. It had a sharp edge and a tender, nodular surface. The hemoglobin content of the blood was 60 per cent, the red blood cell count was 1,500,000, and the white blood cell count 20,000, per cubic millimeter, with 80 per cent polymorphonuclear cells. The value for blood sugar was 200 mg. and that for urea nitrogen 50 mg. per hundred cubic centimeters. The icterus index was 80, and the van den Bergh reaction was of the immediate direct type. At celiotomy, on January 23, biliary obstruction was assigned to a carcinomatous mass high in the hepatic duct, and cholecystostomy was performed. Mesenteric thrombosis, with about 12 inches (26.4 cm.) of hemorrhagic ileum, was also found. The patient died in shock the following day.

Autopsy was performed four hours after death. The combined gross and microscopic diagnoses were: (1) adenocarcinoma of the confluence of the right and left hepatic ducts, with metastases to the regional lymph nodes, (2) hydro-hepatosis, with marked jaundice, (3) multiple hemorrhagic manifestations in the intestine and kidney, (4) surgical wound of the gallbladder, (5) acute degeneration of the myocardium, (6) biliary nephrosis, (7) hyperplasia of the spleen, and (8) hypertrophy of the prostate.

The liver weighed 2,260 Gm. and was yellowish green and tough. The gallbladder contained degenerated blood and disclosed a sutured incision at its fundus. The cystic duct was patulous. The common duct was small and when traced upward ended in an almost total obstruction at the junction of the three hepatic ducts. The obstruction was caused by a small, firm, indurated mass surrounding the ducts and projecting onto the mucous surface as small papillary excrescences. The ducts above the obstruction were enormously distended with clear, light yellow watery bile. The lymph nodes about the common duct were enlarged.

Microscopically, a section through the bile duct at the point of involvement showed the surface of the duct uneven and ulcerated. None of the normal epithelial lining cells remained. The surface was composed of connective tissue, inflammatory cells and tumor tissue which permeated the entire wall of the duct and infiltrated several large nerve fibers. The neoplastic cells were tall columnar, with moderately atypical epithelial elements. The cytoplasm was pink and granular. Most of the nuclei were fairly regular in size, shape and staining, although a few were markedly enlarged. Some cells were flattened and contained small nuclei. Mitotic figures were few. Most of the neoplastic cells were arranged in small acini. Others grew in clumps, strands and nests. The stroma was moderately abundant and infiltrated with mononuclears and lymphocytes. Blood vessels were few, there was little necrosis, and there was practically no hemorrhage.

There were small metastatic deposits in the lymph nodes.



The liver showed the features of biliary stasis, with degeneration and pigmentation in the inner lobule, biliary and focal midzonal necroses, slight bile duct and connective tissue proliferation and round cell infiltration. On the whole, the hepatic parenchyma was not altered markedly.

The kidney showed biliary pigmentation and slight degenerative changes in the tubular epithelium.

CASE 3—P. D., a white man aged 63, was admitted to the Jefferson Hospital on April 16, 1923. There had been gradual loss of weight, strength and appetite for one and one-half years. Nausea with occasional vomiting occurred about once weekly, but pain was never a symptom. Loss of weight and strength was rapid in the five months before admission. Jaundice was first noted on the day before admission. On physical examination the liver was palpable as a nodular, irregular mass filling the epigastrium and the right side of the hypochondrium and extending 5 cm below the costal cage. There was no tenderness or rigidity. The urine was acid, with a specific gravity of 1.005 to 1.012, and contained a trace of albumin, occasional casts, pus cells and bile; it contained no sugar or blood. The Wassermann reaction of the blood serum was negative. The hemoglobin content of the blood was 88 per cent, the red blood cell count was 3,900,000 and the white blood cell count 8,200 per cubic millimeter, and the color index was 1.12; about a month later these values were respectively 83 per cent, 3,500,000, 6,000 and 1.18. Analysis of the gastric contents showed a total acidity of 10 to 26, free hydrochloric acid of 9 and 12 at forty-five and sixty minutes respectively and absent in all other specimens, there were a trace of lactic acid and a trace of bile in all specimens, the latter indicating incomplete biliary obstruction. Roentgen examination of the gastrointestinal tract after a barium sulfate meal was performed on April 23 and showed a filling defect in the antrum of the stomach, producing irregularity of the sphincter. The stomach appeared irregular in outline, displaced to the left and fixed. At the end of six hours a medium amount of residue was present, and the duodenum appeared normal. The diagnosis was advanced carcinoma involving the lesser curvature of the antrum of the stomach. The temperature varied from 96 to 99 F, the pulse rate from 60 to 86 and the respiratory rate from 20 to 30. The patient left the hospital unimproved on June 4 and returned to work for three months. Then, because of increasing weakness, he entered the Philadelphia General Hospital on September 21. Death occurred one week later.

Autopsy was performed eighteen hours after death. The combined gross and microscopic diagnoses were (1) primary adenocarcinoma of the common hepatic duct, with metastasis to the liver, (2) hydrohepatosis, with marked jaundice, (3) calculous cholecystitis, (4) infarcts of the spleen, (5) biliary nephrosis, (6) arteriosclerosis of the aorta and the coronary arteries, (7) terminal pneumoma, (8) myocardial degeneration, (9) peritoneal effusion, and (10) hyperplasia of the prostate gland.

The peritoneal cavity contained 6 liters of dark yellow serofibrinous fluid.

The liver weighed 2,830 Gm. It was firm, dark green and granular. The lobular markings were indistinct and the lobules were surrounded by gray tissue. The lower third of the organ was occupied by a firm white growth 12 cm in length extending for 6 cm from the lower margin into the liver tissue. The cut surface of the tumor was white, dry and fibrous. In the hepatic duct near its origin the primary tumor was found as a walnut sized soft white nodule which projected into the lumen of the duct and merged with the larger mass within the liver.

The gallbladder was normal in size and contained tarry bile and several small friable calculi, similar calculi were present in the common bile duct

The pancreas showed no visible change

The prostate contained a number of small fibrous nodules

The intestines showed congestion and edema of the mucous membrane

Microscopically, the single section showing neoplasm was largely composed of connective tissue containing a large vein, a nerve and a necrotic area resembling liver tissue Throughout the section were scattered nodules of atypical epithelial

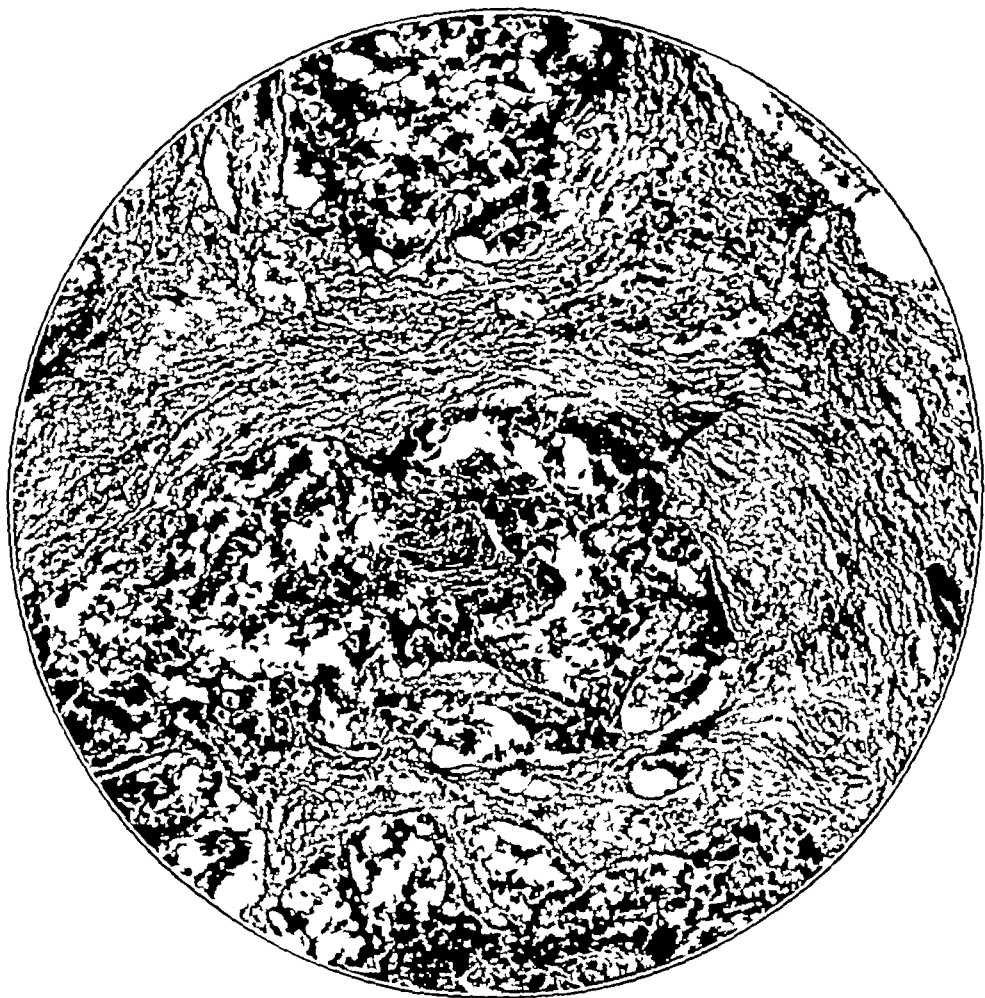


Fig 4 (case 3) —Microscopic section of the tumor, showing scattered nodules of atypical epithelial cells embedded in dense hyalinized connective tissue  $\times 100$

cells These nodules were fairly uniform in size and structure The atypical epithelial cells were columnar or cuboidal, with deeply stained granular cytoplasm and large, fairly regular hyperchromatic nuclei, mitoses were rare The nodular areas were composed of atypical epithelial cells arranged as acini or growing solidly In the larger nodules one half to two thirds of the inner portion was necrotic and contained blue-staining deposits (fig 4) The stroma adjacent to the tumor cells was dense and collagenous, but elsewhere it was loose, vascular and infiltrated with inflammatory cells in focal areas

The liver showed marked pigmentation and slight degeneration in the inner part of the lobule, with moderate fibrosis, bile duct proliferation and slight irregularity of the surface

#### AGE AND SEX INCIDENCE

Of the 35 patients, 29 were men ranging in age from 29 to 82 years, with an average of 56.5 years, and 6 were women ranging in age from 31 to 59 years, with an average of 45.2 years. In the younger age group were 2 men, aged 29 and 32 respectively, and 1 woman, aged 31.

Three cases of primary carcinoma of the hepatic duct were found in a series of 22,152 autopsies performed at the Philadelphia General Hospital between Jan. 1, 1920 and Dec. 31, 1936, an incidence of 0.0135 per cent of all autopsies. Carcinoma was found in 2,687 cases in this series, an incidence of 0.11 per cent of all carcinomas.

#### MORBID ANATOMY

The neoplasms in this series of cancer of the hepatic ducts can be divided into three groups on the basis of the morbid anatomic characteristics, namely, local (26 cases), diffuse (in 8 cases) and combined local and diffuse (in 1 case).

A local tumor was present in the following sites: at the bifurcation of the common hepatic duct (13 cases), at the bifurcation of the common hepatic duct and the lower portions of the two ramæ (6 cases), at the lower end of the common hepatic duct (4 cases), and at the left hepatic ramus (2 cases). In 1 case the location was not stated. The bile ducts were completely obstructed by neoplasm in 13 cases and incompletely obstructed in 5, in the remainder this point was not investigated. In 4 cases the local tumor consisted of a soft, friable polypoid nodule, firmly attached to the wall of the duct by a pedicle or a broad base and elevated above the mucous surface so as to fill the lumen. The majority of the local tumors, however, were small, annular, constricting gray or yellowish white growths averaging 2 cm. in diameter, with thickening of the wall of the duct up to 2 cm. The mucous surface was either smooth or finely granular, excrescences or fissures and ulceration were observed in 4 cases. Externally, a well defined tumor mass was usually observed, which in 1 case extended into the liver as a wedge-shaped nodule. In several cases the lesion on palpation was mistaken for a gallstone. In others it was suggestive of benign fibrous stricture, one operator dilated it in the mistaken belief that he was dealing with a chronic inflammatory process. The two tumors originating in the left hepatic duct were apparently of this type. In Rocco's case, a small, hard, stenosing carcinoma of the left hepatic duct permitted the passage of a fine sound. In McLaughlin's case 4, a firm yellowish white tumor completely surrounded and invaded the left hepatic duct almost occluding its lumen.

A probe forced through this mass met with an obstruction 2 cm above the bifurcation of the common hepatic duct, and withdrawal was followed by the discharge of thick, purulent matter from above, the right hepatic duct was distended, and its orifice at the junction with the left branch was almost completely occluded by tumor

The diffuse type of growth was found in the region of the bifurcation of the common hepatic duct in 1 case, in the region of this bifurcation and extending upward along the two ramæ in 6 and involving the entire length of the common hepatic duct in 1. The neoplastic involvement in these cases was diffuse and widespread, and the peripheral limits were ill defined. The neoplastic tissue was firm, white and annular, producing marked stenosis and rigidity of the ducts, while the mucosa was granular, fissured and sometimes ulcerated. In several instances the growth extended along the large bile ducts into the liver, forming either a continuous large solitary mass or multiple pea-sized nodules.

A combined local and diffuse type of growth occurred in Korczynski's case. The wall of the beginning portion of the common hepatic duct was 2 mm thick, and on its inner surface were diffuse deposits of a rather soft, succulent reddish yellow tissue. About 2 cm below these was a 4 mm tumor on the mucous surface.

In no case in this group was there neoplastic involvement of the cystic duct or of the common bile duct. The cystic duct was partially compressed by extrinsic masses in 1 instance, and in another the base of the cystic duct was completely obliterated by chronic inflammatory scar tissue. Biliary calculi were present in eight locations in a total of 5 cases, in the gallbladder in 4, in the common bile duct in 2 and in the cystic and intrahepatic bile ducts in 1 each. The fluid in the distended ducts proximal to the point of obstruction was described as clear and white in 3 cases and purulent in 1.

The liver showed some degree of biliary stasis in all cases, hepatic enlargement in the majority and biliary cirrhosis in 9. Hepatic abscesses were reported in 1 case, purulent cholangitis in 2 and subphrenic abscess in 1. Multiple white infarcts were present in the liver in 1 case. The finding of hepatic infarction is extremely unusual, for of a large number of cases of obstructive jaundice in human beings examined by two of us (Lieber and Stewart) and from a review of the literature on hepatic infarction (Lund, Lieber and Stewart) this was the only clinical example of an infarct of the liver encountered in the presence of biliary stasis. In animals, on the contrary, infarcts of the liver are not uncommon after experimental ligation of the common bile duct (Stewart and Lieber).

Usually the gallbladder contained watery gray, white or opalescent fluid and was not distended. In 1 case the content was thin icteric fluid.

and in another, thick tarry bile. This indicated either incomplete obstruction at the level of the tumor or that accessory ducts passed directly from the liver into the gallbladder. No case was found in which such accessory ducts obviated the full effects of biliary stasis. The gallbladder was empty and collapsed in 2 cases and distended in 7 cases, in all of which the cystic duct emptied below the primary tumor. The mechanism responsible for cholecystic distention was unexplained, although blockage of the cystic duct may have been effected by traction of the primary tumor or by compression due to extrinsic pressure (e g., by enlarged lymph nodes). In 1 case it was obliterated by scar tissue. The contents of the gallbladder were blood stained in 3 cases, in 1 of which an incision had been made previously. Evidences of cholecystitis with atrophy were present in 9 cases, in 4 of which biliary calculi were also found. Pericholecystic adhesions were present in several instances.

Free fluid in amounts of 1 to 6 liters was present in the peritoneal cavity in 11 cases, in the majority it was bile stained. The effusion in 1 case contained blood. In 2 cases there was evidence of recent fibrinous peritonitis.

Neoplastic spread occurred in 17 cases, as follows: to the liver (12 cases), to the regional lymph nodes (7 cases), and to the pancreas, the gastrohepatic ligament and the mediastinum (1 case each). In 10 cases of hepatic invasion the tumor extended directly along the lesser ducts into the liver. In 1 instance the hepatic extension consisted of a single large, firm mass 12 by 6 mm directly continuous with the primary growth. Discrete metastases were noted in the liver in the cases reported by Rocco and by Walters and Olson.

#### HISTOLOGIC PICTURE

All the neoplasms were glandular carcinomas. In the majority, the atypical epithelial cells were cylindric or cuboidal. Some degree of pleomorphism was present in 5 cases, in 1 of which the tumor was described as a solid alveolar carcinoma. Giant cells were present in 1 case. Nuclear hypertrophy and hyperchromasia were usual. Mitotic figures were noted in only 4 cases. Acinar structures were present in 27 cases, with marked variation in size and shape in several and the formation of microcysts in 2. Papillary projections into the acini occurred in 4 cases. Mucinous material was present in varying amount within and between the cells and within the acini in 4 cases, in 2 of which the tumors were designated as mucinous adenocarcinoma. Perineural invasion occurred in 2 cases. The stroma was abundant in the majority, the scirrhous character being an outstanding feature. Areas of hemorrhage, necrosis or inflammatory reaction were rarely described.

## CARCINOMA OF THE CYSTIC DUCT

Twenty-seven cases reported as examples of primary carcinoma of the cystic duct were abstracted from the literature. These were studied critically to eliminate the gallbladder and other sites as possible primary sources of the neoplasm. These reported primary neoplasms of the cystic duct were grouped as follows:

*Group I*—In 14 cases of tumors in the cystic duct there appeared also to be gross neoplastic involvement of the gallbladder, confirmed microscopically in 5 instances (Vautrin, Chini, Lcini, Pellegrini, Dalla Valle, case 2, Satta, cases 1 and 2, Schmidt, Ortiz and Coffigny, Dialti, Cailliau, Ramlau-Hansen, case 2, Shapiro and Lifvendahl, case 15, and Hess and Faltitschek, case 3).

*Group II*—In 7 cases, histologic studies of the neoplasm in the cystic duct or in the gallbladder were lacking. The latter organ was described only once, the wall of the gallbladder was thickened, but the mucous membrane appeared normal (Rosch, Etienne, McGlinn, cases 3213A and 839B, Dalla Valle, case 3, Bertini, Bailey).

*Group III*—In 5 cases, although gross and microscopic studies were made of the neoplasm in the cystic duct, microscopic studies of the gallbladder were lacking. The gallbladder was described grossly in only 1 case, in which it was small and thick (Petren, case 46, Wohlwill, Saltykow, case 8, Hellner, McLaughlin, case 1).

*Group IV*—In 1 case a small localized polypoid tumor of the cystic duct was found, together with metastases in the liver, in the abdominal lymph nodes, in Virchow's node and in the rectal wall. The neoplasm was designated histologically as carcinoma solidum. The gallbladder was not described grossly or microscopically and it appears that the rectum was insufficiently considered as a possible primary source for the growth (Shapiro and Lifvendahl, case 14).

We are, therefore, unable to consider any of these cases as indisputable instances of primary carcinoma of the cystic duct. Obviously, extreme care must be taken to exclude cancer of the gallbladder, pancreas, stomach, duodenum and rectum in order to substantiate the case. Occasionally primary carcinoma of the gallbladder infiltrates the cystic, hepatic and common bile ducts and even extends down through the ampulla of Vater into the duodenum. Neoplasms at the confluence of the bile ducts (to be dealt with in the next section) possibly may have taken origin from the cystic duct, secondarily extending to the hepatic and common bile ducts. However, no proved case has yet been reported of a malignant growth arising primarily in the cystic duct and remaining sufficiently localized within the confines of that structure to make the origin of the tumor unquestionable.

## CARCINOMA AT THE CONFLUENCE OF THE EXTRAHEPATIC BILE DUCTS

Two new cases of carcinoma at the confluence of the common hepatic duct, the cystic duct and the common bile duct are reported. One hundred and forty cases were abstracted from the literature, 46 of which were regarded as acceptable,<sup>5</sup> the report of each including a clinical history and gross and microscopic studies of the primary lesion. Twelve additional cases, although probably authentic examples of this condition, were not included in the present study owing to the lack of a clinical history or to insufficient details.<sup>6</sup> Forty-seven cases were not utilized because histologic studies were lacking.<sup>7</sup>

Of 35 cases, the possibility remained that the neoplasm was primary in the gallbladder in 32 cases<sup>8</sup> and in the stomach in 3.<sup>9</sup> The reports of the 2 new cases follow, and the data obtained from these, together with those from the 46 acceptable cases of this condition, are subjected to analysis and summary based on a total of 48 cases in this group.

CASE 4—M. M., a white man aged 64, was admitted to the Philadelphia General Hospital on July 11, 1927, with deep jaundice and extreme emaciation. A detailed history was not obtained because of difficulties with language. The present illness had begun eight months previously. Pain had not caused complaint.

5 Laugier, Choupe, Silver, Schreiber, Bradbury, Yamagiva, case 1, Brenner, case 1, Bruno, Lecene and Pagniez, cases 1 and 2, Devic and Gallavardin, case 2, Koerber, Ulszewski, case 2, Miodowski, case 6, Huguenin, Kehr, Donati, Scagliosi, case 1, Pepere, Weber and Michels, Löschke, Cade and Pallasse, Borelius, case 1, Wising and Key, Morian, case 1, Spindler, Lameris, Pallin, case 4, Prat, case 2, Dalla Valle, case 1, Wahl, case 5, Senokuchi, Kurths, Vallery, vander Veer, Pliveric, Carnot, Mondor, Shapiro and Lifvendahl, case 13, McLaughlin, cases 2 and 3, Lee and Totten, case 1, Cabot, case 21, 122, Romano and Rey, Quenu and Gasne, Cabot, case 22492.

6 Moore, case 2, Brenner, Jordan, Cotte, Saltykow, case 5, Nystrom, Duplant, Thevenod and Finck, Shapiro and Lifvendahl, case 7, Konjetzny, Fehr, La Manna, case 4.

7 Durand-Fardel, Bourceret and Cossy, Aufrecht, case 2, Bernheim and Simon, case 2, Niemeyer, Bohnstedt, de la Camp, cases 2 and 3, Geraudel, Tesson, Patel and Jaboulay, Tuffier, Gallavardin, Junquet, cases 9 and 10, Warfvinge and Wallis, Åkerbloom, Berg, Stueda, case 5, Littlewood, Pallasse and Perret, Desjardins, Flugger, Dressen, Petren, case 18, Koechlin, case 2, Amberger, Dalla Valle, cases 5, 6, 7, 8, 9, 10, 11 and 12, Copello, Brocq and Maduro, cases 2 and 3, Cabot, case 13521, Blomstrom, case 1, Cabot, case 16071, Ferrario, Ramlau-Hansen, cases 3 and 4, Payan, Monges and de Vernejoul, Romano and Rey, case 2, La Manna, case 3.

8 Frarier, Remy, Haas, cases 1 and 2, Fazio, Anderson and Dewar, Jourdan, Brunswick, Kleinertz, Häni, cases 5 and 6, Miodowski, cases 2 and 3, Planteau and Cochez, Martin, case 2, Sherrill, cases 1 and 2, Lecene, Cailhau, Zuccola, case 5, Saltykow, case 6, Dalla Valle, cases 2, 3 and 4, Brocq and Maduro, case 1, Dimitriu, Gutierrez, Ramlau-Hansen, case 1, Chabrol and Waitz, Perez Fontana, Anastasia and Castro, Lamattina, Bailey, case 18.

9 Haas, case 3, Griffon and Leven, Gleiss.

The abdomen was prominent and bulging, a mass was present in the right side of the hypochondrium, and there was evidence of free peritoneal fluid. The chest was emphysematous. Resonance at the base of the left lung posteriorly was impaired. Edema of the lower extremities was marked. The urine was alkaline, its specific gravity was 1.012, and it contained a faint trace of albumin and occasional hyaline casts. The van den Bergh reaction was positive, and the icteric index was 150. Paracentesis yielded 4,000 cc of icteric fluid. The temperature varied from 97 to 98.3 F, the pulse rate from 70 to 88 and the respiratory rate from 20 to 28. The clinical diagnosis was carcinoma of the head of the pancreas. The patient died on July 18.

Autopsy was performed four hours after death. The combined gross anatomic and microscopic diagnoses were (1) carcinoma of the extrahepatic bile ducts, with metastases to the lymph nodes, the liver and the peritoneum, (2) hemorrhagic peritoneal effusion, (3) hydrophepatosis, with marked jaundice, (4) intestinal hemorrhage, (5) bile pigmentation of the kidney, (6) cystic goiter, (7) dilatation and degeneration of the heart, and (8) terminal pneumonia.

The peritoneal cavity contained 3,500 cc of bloody fluid. Many small gray nodules studded the peritoneum of the small and large intestine, diaphragm and pelvis. The pericardial cavity contained 50 cc of bile-stained fluid.

The liver weighed 1,530 Gm. The surface was finely granular, the edges were sharp and the parenchyma was dark green, firm and tough. A number of firm gray circumscribed nodules were superficially located beneath the capsule. The branches of the portal vein and bile ducts were tremendously dilated. The gallbladder contained a small amount of brown viscid fluid. A very narrow lumen could be traced through the common bile and hepatic ducts, and the cystic duct was totally obstructed. Near the ampulla of Vater the lumen of the common bile duct again widened. Along the course of the obstruction the walls of the affected ducts were replaced by tough, gray homogeneous tissue of cartilaginous consistency.

The lymph nodes along the greater curvature of the stomach were enlarged and on section were gray and homogeneous.

A microscopic section was obtained of the bile duct and an adherent piece of colon. The inner surface of the duct was uneven and ulcerated in places. The surface cells showed autolysis, but immediately beneath were atypical epithelial elements and inflammatory cells. The wall of the duct was markedly thickened by dense fibrous tissue, which was infiltrated by atypical epithelial cells. The line of adhesion between the bile duct and the colon was infiltrated by tumor tissue, as was the outer coat of the colon, but the intestinal mucous membrane was intact. The tumor cells consisted of atypical columnar epithelium arranged in the form of acini. Many were flattened and irregular in size, shape and staining. The nuclei were large, oval and frequently pale and the cytoplasm was pink and granular. A few mitotic figures were observed. Irregularity of the tumor cells appeared greatest where they permeated the dense connective tissue wall of the bile duct. Some cells contained single large vacuoles. Most acini were small and varied in shape, with degenerated material in the center. The connective tissue stroma was abundant, vascular and infiltrated with focal collections of lymphocytes.

The kidneys showed marked bile pigmentation and slight degenerative changes in the tubular epithelium.

The liver showed the features of far advanced biliary obstruction, with pigmentation and degeneration in the inner portion of the lobule, focal midzonal and biliary necrosis, proliferation of small bile ducts and marked cirrhosis, with irregularity of the lobular architecture.



CASE 5—J R, a white man aged 75, was admitted to the Philadelphia General Hospital on Sept 3, 1921, complaining of painless progressive jaundice, increasing weakness and loss of appetite for five months. The jaundice varied somewhat in intensity but never completely disappeared. Recently there had been marked pruritus. The stools were clay colored during all this period, but there was no constipation or diarrhea. A mass the size of a hen's egg lay in the right upper abdominal quadrant, but neither the liver nor the spleen was palpable. There was no fever at any time. The urine was alkaline, had a specific gravity of 1.010 and

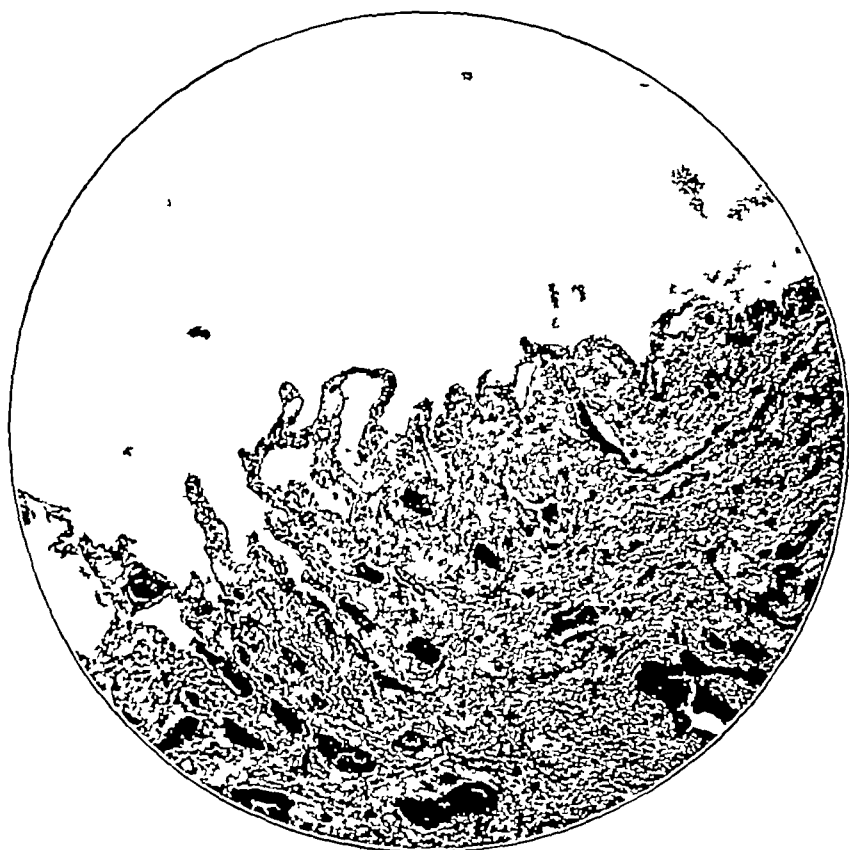


Fig 5 (case 5)—Bile duct, showing numerical increase and hypertrophy of surface villi and collections of atypical epithelial cells below the surface. In a few places narrow fissures extend into the depths of the wall.  $\times 50$

contained bile. A clinical diagnosis of carcinoma of the head of the pancreas was made. The jaundice deepened, and increasing evidence of ascites was noted, weakness was progressive, and the patient died on September 23.

Autopsy was performed four hours after death. The combined gross and microscopic diagnoses were: (1) adenocarcinoma primary at the confluence of the common cystic and hepatic ducts, with extension to the pancreas, (2) hydro-hepatosis with marked jaundice, (3) biliary cirrhosis of the liver, (4) biliary nephrosis, (5) generalized passive venous congestions, (6) anasarca and (7) arteriosclerosis of the aorta and the coronary arteries.

The peritoneal cavity contained 1,000 cc of slightly turbid fluid, and the serosa was smooth and glistening. It was not possible to express bile into the duodenum by pressure on the gallbladder. A probe passed up the common bile duct encountered an obstruction 4.5 cm from the ampulla of Vater. The gallbladder was enormously distended with clear, colorless fluid. It measured 19 cm in length. The cystic duct was also distended, and its outlet into the common bile duct was completely blocked. The hepatic duct was distended with clear yellow bile. It was totally obstructed by a firm tumor 5 cm in length and 2 cm wide, this arose 4.5 cm from the ampulla and obstructed all three ducts at the confluence. Here the mucosa was thickened by tumor tissue which extended for a short distance into the pancreas. The liver weighed 2,130 Gm. The cut surface was green, the lobular markings prominent and the bile ducts markedly dilated.

A section of the bile duct, obtained through an area showing malignant transformation, was studied microscopically. Most of the epithelium along the normal portion of the duct was autolyzed. There was an increase in number and hypertrophy of the surface villi, and in the stroma of these were collections of atypical epithelial cells. In a few places narrow fissures extended into the depth of the wall of the duct, but no ulceration was observed here (fig 5). Many atypical epithelial cells were tall and columnar, having abundant acidophilic granular cytoplasm and basally situated hyperchromatic nuclei. Other cells varied considerably in size, shape and staining and tended to become flattened, especially where the acini were distended. Other cells grew in nests and strands which permeated between the connective tissue fibers through the entire thickness of the duct and into the lymphatic vessels. Mitotic figures were infrequent. The stroma was abundant and dense, containing few vessels. Necrosis and hemorrhage were slight, and there were no marked inflammatory changes.

The liver showed advanced biliary cirrhosis. The lobular architecture was distorted, the central veins were displaced, and the cords of the cells were irregularly arranged. There was marked proliferation of small biliary ducts and of connective tissue which invaded the lobules. The medium-sized bile ducts were distended, and their walls were thickened and fibrotic. The parenchymal and phagocytic cells of the liver were deeply pigmented. The hepatic cells were degenerated and atrophic, and many areas of biliary necrosis were seen.

#### AGE AND SEX INCIDENCE

The patients in the reported cases included 32 men ranging in age from 45 to 81 years, with an average age of 61.5 years, and 16 women ranging in age from 38 to 72 years, with an average age of 64.7 years.

The 2 cases of carcinoma of the confluence of the ducts occurred at the Philadelphia General Hospital in a series of 22,152 autopsies (0.009 per cent), of which 2,687 showed carcinoma (0.074 per cent of all carcinomas).

#### MORBID ANATOMY

The common hepatic, cystic and common bile ducts were involved jointly by neoplasm in 38 cases. Of the remaining 10 cases there was no mention of involvement of the cystic duct in 6 or of the hepatic

duct in 2, whereas in 2 cases the cystic duct was said to be entirely free of neoplasm. In Schreiber's case, although a cherry-sized tumor projected into the lumen of the common bile duct at the point of union with the hepatic and cystic ducts, the cystic duct was patent and opened just below the involved hepatic duct. In Miodowski's case 6, the common hepatic duct was the seat of an annular tumor the size of a goose egg, which extended downward to involve the common bile duct, between these two areas of involvement, however, a 3 mm segment of the bile duct was curiously free from neoplasm and corresponded exactly to the point of entrance of the cystic duct.

The neoplasm formed a local tumor in 27 cases and a diffuse growth in 21.

The local tumors were of two types. One consisted of a single elevated nodular projection above the mucous lining. The other type caused annular constriction and thickening of the wall of the duct, occasionally flat excrescences formed on the mucous surface, but no elevated projection was described. Most of the local tumors were said to be the size of a hazelnut, a few were pea sized, and two were the size of a hen's egg. The only stated measurement was 5 by 2 by 2 cm. The tumors were gray or white and hard, fibrous or cartilaginous in consistency. The surface was slightly roughened, granular or papillary, and was raw and necrotic in a few instances. In 2 cases the mucous membrane was smooth, and the tumor was thought to arise from glands in the wall of the duct. In 1 case a localized, elevated nodule exhibited a ball-valve action which arrested a sound passed from below but not one passed from above. An incorrect diagnosis of biliary calculus was made at laparotomy in 2 cases. The rate of growth of the neoplasm was recorded in 2 instances by direct inspection through a laparotomy incision. One tumor did not enlarge perceptibly during six months, the other grew from the size of a walnut to that of a hen's egg in nine months.

The diffuse type of neoplastic involvement was characterized by excessive thickening of the wall of the duct by gray, white or yellowish white firm, fibrous or cartilaginous tissue. Peripherally this type of growth was poorly defined. In 1 case tumor tissue extended into the transverse fissure of the liver. The lining of the duct in the involved portion was either smooth or studded with diffuse excrescences friable vegetations soft polypoid masses (varying in size from that of a cherry to that of a goose egg) and small ulcers. Sometimes the lesion was mistaken grossly for a benign fibrous stricture of inflammatory origin.

The bile ducts were completely obstructed in 8 cases incompletely obstructed in 18 and probably incompletely obstructed in the remainder. Since it is difficult precisely to determine the patency of bile ducts at

postmortem examination, the accuracy of these figures is questionable. Clinical data may indicate complete obstruction, and yet evidence of patency may appear at autopsy. The upper limit of obstruction occurred in the lower segment of the common hepatic duct in 37 cases, in the mid-duct in 2 and at the upper end of the duct in 4. In the remaining 5 cases the point of obstruction extended to the left hepatic ramus in all and to the right hepatic ramus in 2. Above the obstruction the bile ducts were thin and maximally dilated. The dilatation extended upward involving the lesser intrahepatic radicles, and occasionally formed varicosities on the surface of the liver. The contents of the intrahepatic ducts were light green or yellow in 6 cases, clear and colorless in 3 and purulent in 2. The liver usually was enlarged and showed the gross characteristics of biliary stasis. Marked cirrhosis was present in 10 cases, in 2 of which the liver was small. Hepatic abscesses were present in 3 instances.

The lower limit of obstruction was variable. Below this limit the common bile duct regained its usual caliber, its mucous membrane was smooth, usually not bile stained and sometimes covered with clear mucus.

The orifice of the cystic duct was completely obstructed in 35 cases, partially obstructed in 5 and uninvolved in 2. In 6 this point was not commented on. In 1 case the entire length of the cystic duct was totally obliterated by scar tissue, so that not even its lumen could be identified with certainty. In 3 others this duct was obstructed by a combination of calculus and neoplasm. Proximal to the point of closure the cystic duct and gallbladder were distended in 25 cases. The gallbladder averaged about twice normal in volume, being 19 cm. long in 1 case and the size of a man's fist in another. It contained from 50 to 500 cc. of fluid, which was white or colorless in 12 cases, light colored in 8 and thick and tarry in 2. With tarry bile in the gallbladder, the possibility of a ball-valve action of the neoplasm was considered as permitting bile to enter the viscus and become concentrated there but not to leave it. The other alternative postulates an anomalous duct from the liver discharging bile directly into the gallbladder and thus circumscribing the obstruction of the cystic duct. The contents of the gallbladder were purulent in 3 cases and thick yellow and inspissated in 2. In 13 cases, the viscus was either undistended or small and atrophied, and the cystic duct was completely obstructed in all but 3 of these. Biliary calculi were present in the gallbladder in 9 cases, in the cystic duct in 2 of these and in the cystic duct only in another case. Evidences of cholecystitis were recorded in 10 cases, with empyema of the gallbladder in 4 and associated calculi in 4 others. In 1 case, a rent 2 by 1 cm. was present on the posterior surface of the gallbladder, the viscus was empty and 2 liters of partially clotted blood was free in the abdominal cavity.

Peritoneal effusions occurred in 13 cases in amounts of 1 to 4 liters of fluid, with bile in 3, blood in 2 and inflammatory elements in 3, in 1 of which the material was frankly purulent. In Senokuchi's case, the abdominal cavity was filled with 2,000 cc of colloid-like material, and the serosa was everywhere covered with colloid masses mixed with fibrinous and fibrous strands resulting in extensive visceral adhesions. In the upper part of the abdomen, adhesions were present in 10 cases, to the liver, the gallbladder, the colon, the anterior abdominal wall and the great omentum. Fibrinous adhesions were present in 4 cases, in 2 following laparotomy.

Extensions or metastases of the primary tumor were found in 22 of the 48 cases and were distributed as follows: in the liver (16 cases), in the regional lymph nodes (10 cases), in the gallbladder (2 cases), in the lung (2 cases), in the peritoneum (2 cases), and in the pancreas, the kidney, the wall of the portal vein, the gastrohepatic ligament, the spleen and the bronchial lymph nodes (1 case each). The hepatic metastases were in general similar to those from other neoplasms of the alimentary tract. In a few cases direct infiltration of hepatic substance resulted from growth along the ramus of the hepatic duct. In Senokuchi's case of mucinous carcinoma there were extensive peritoneal involvement and metastases to the spleen. The 2 cases in which there were metastases to the gallbladder are of interest. In McLaughlin's case 2, the gallbladder was small and thick walled, and in one area, near the fundus, the mucous membrane was yellowish white and elevated above the general surface level, it was adherent to an underlying dense tumor nodule continuous with the adjacent liver tissue. Microscopic examination showed extension of carcinoma from the liver into the gallbladder, with involvement of all coats except the mucosa. Similarly in Cade and Pallasse's case, the gallbladder was dilated and tense, and at its external superior pole a neoplastic nodule united it with the liver.

#### HISTOLOGIC PICTURE

All the neoplasms at the confluence of the bile ducts were glandular carcinomas. The cells were essentially cylindric, columnar or cuboidal, although in many cases they were flattened, and in 1 instance goblet cells were noted. Pleomorphism was marked in 8 cases, and one neoplasm was entirely undifferentiated. The cells reproduced acinar structures in 37 cases, with papillary infoldings in 3, they grew in the form of clumps, strands, cords or nests in 20 other cases. Mitotic figures were observed in only 6 cases. Considerable quantities of mucinous material occurred in and between the cells and in the acini in 3 cases in all of which the tumors were designated as mucinous adenocarcinomas. Marked dilatation of acini with the formation of microcysts

was observed in a single case. The stroma of these tumors was usually abundant, although a few solitary pedunculated growths were only sparsely supported by connective tissue. Small areas of hemorrhage and necrosis were rarely observed, and there was little inflammatory reaction. Tumor cells occasionally extended into the perineural tissues and blood vessels. In 1 instance the main trunk of the portal vein was thrombosed. Feh's case, not included in this study because the clinical history was lacking, is nevertheless interesting, for the neoplasm was constructed of tubules and strands of cylindric and low cuboidal cells together with large nests of epidermoid carcinoma growing independently or intermingled with the glandular cells. These nests consisted of squamous epithelial cells, often arranged concentrically and producing epithelial pearls.

#### CARCINOMA OF THE COMMON BILE DUCT

Included in this group are only those cases of carcinoma in which the tumor definitely originated in the common bile duct, between the orifice of the cystic duct and the ampulla of Vater and not involving either of these structures. The neoplasms arising in and about the papilla and ampulla of Vater have been considered in a previous communication (Lieber, Stewart and Lund). One new case of primary carcinoma of the common bile duct is reported. Eighty-six cases of this condition were abstracted from the literature, 20 of which were regarded as acceptable on the basis of a clinical history and gross and microscopic studies of the primary lesion<sup>10</sup>. Fifteen additional cases, although probably authentic, were not included because of lack of a clinical history or because of insufficient details<sup>11</sup>. Fifty-one cases were discarded for the following reasons. In 38 cases<sup>12</sup> no histologic examination of the primary lesion was reported, the diagnosis apparently being based on

10 Ormerod, Chappet de la Camp, case 1, Griffon and Dartigues, Durand-Fardel, Devic and Gallavardin, case 1, Ulszewski, case 1, Borelius, cases 2 and 3, Morian, case 4, Leclerc, Bret and Dufourt, Petren, cases 20 and 22, Dalla Valle, cases 1 and 3, Shapiro and Lifvendahl, case 10, Cabot, case 16261, Demel, Pangaro, case 1.

11 Birch-Hirschfeld, cases 1 and 2, Moore, case 1, Hebb, Rolleston, cases 10 and 11, Quensel and Vestberg, Gianelli, Saltykow, cases 2 and 4, Schüssler, case 4, Dalla Valle, case 2, Mosto, cases 1 and 2, and Shapiro and Lifvendahl, case 9.

12 Durand-Fardel, Segond, Delafield, Kraus, Herringham, case 18, Peck, Brenner, case 2, Pennato, case 2, Dobrovici and Fair, Arnsperger, case 26, Goldammer, cases 216, 218, 219 and 220, Schaffner, Stieda, case 14, Koerber, case 1, Schmidt, case 1, McGlinn, cases 1022A and 3037A, Paus, cases 211 and 215, Cheney, Zuccola, case 1, Poynton, Petren, case 1, Castex, Schussler, case 2, Fargue, Roux and Milhaud, Dalla Valle, cases 4, 5, 6, 7, 8 and 9, Murgoci, case 2, Blomstrom, case 4, Bettoni, case 1.

gross inspection alone, in 13 cases<sup>13</sup> the ductal origin of the neoplasm was not established with certainty in the presence of involvement of the pancreas in 4, of the stomach in 3, of the gallbladder in 3, of the rectum in 2 and of the cecum in 1, since any of the organs may have been the primary source of carcinoma. Thus there is a total of 21 cases in this group.

CASE 6—E S, a white woman, was admitted to the Jefferson Hospital in 1912 for chronic nephritis, in 1928 for cataract, in 1929 for drainage of an abscess of the liver with partial cholecystectomy and cholecystostomy, in 1930 for an incisional hernia and multiple intestinal adhesions and in 1933 for ulcerative cystitis. Her last admission to the hospital, at the age of 76, was on July 26, 1934. There were loss of appetite, epigastric pain, jaundice, belching and abdominal tenderness of three months' duration. The pain was continuous and dull and did not radiate. Examination revealed obesity, marked jaundice and stupor. The abdomen was prominent and showed the scars of previous operations. The liver was palpable 4 fingerbreadths below the costal margin, in the midclavicular line, and was tender and smooth with rounded edges. The temperature varied from 97.2 to 100.4 F, with a sharp rise to 104.6 F shortly before death. Roentgen examination was performed on two occasions and showed a walnut-sized shadow in the right upper abdominal quadrant, not definitely in the gallbladder and interpreted as a calcified mesenteric lymph node. Duodenal drainage on one occasion failed to yield bile. The hemoglobin content of the blood was 68 per cent, the red blood cell count was 3,500,000 and the white blood cell count 6,000 per cubic millimeter, the color index was 0.9, the bleeding time was three minutes, and the clotting time was four minutes. The Wassermann and Kahn reactions on the blood serum were negative. The nonprotein nitrogen content of the blood was 36.14 mg and the sugar content 82 mg per hundred cubic centimeters. A test of hepatic function with bromsulphalein showed 80 per cent retention of the dye at the end of thirty minutes (2 mg dose). The reaction to the direct van den Bergh test was positive, and the value for serum bilirubin was 26 mg per hundred cubic centimeters. The urine was variably acid and alkaline, with a specific gravity of 1.014 to 1.022, and contained a trace of albumin. The patient's course in the hospital was characterized by progressive increase of jaundice, repeated vomiting, increasing weakness and death on August 28.

Autopsy was performed seventeen hours after death. The combined gross and microscopic diagnoses were (1) adenocarcinoma of the common bile duct, with extension to the pancreas and metastasis to a regional lymph node, (2) hydro-hepatosis, with biliary cirrhosis and marked jaundice, (3) chronic cholecystitis and rupture of the gallbladder, (4) fatty infiltration of the pancreas, with fat necrosis, (5) extensive peritoneal adhesions, (6) marked generalized arteriosclerosis, (7) siderotic deposits in the capsule of the spleen, (8) fibrosis and fatty infiltration of the myocardium, (9) coronary occlusion, (10) chronic nephritis, and (11) bronchopneumonia.

There was an old healed scar in the right upper quadrant of the abdomen. The intra-abdominal structures were obscured by dense peritoneal adhesions extending between the liver, the gallbladder, adjacent portions of the gastro-

13 Van der Bui, Stuegle, Häm, case 7; Rousseau and Morin, Murchison, Van Gieson, Burnham and Simon, case 1; Moschowitz, Schonbauer and Bitch, case 5; Secco and Pungaro, Shapiro and Lifvendahl, case 5; Nochmowski, case 3; Miodow, case 5.

intestinal tract and the anterior abdominal wall. In an attempt to separate these adhesions a cystic area was broken into, which yielded a large quantity of thick, dark green granular fluid. The ampulla of Vater was patent and admitted both the pancreatic and the common bile duct, both of which were slightly dilated but emptied freely into the intestine. Two centimeters above the ampulla the common bile duct was tightly strictured by a thickened, indurated mass. At the point of involvement the lumen was not completely obliterated, for a small amount of dark green fluid could be forced past the obstruction by pressure on the ducts above.

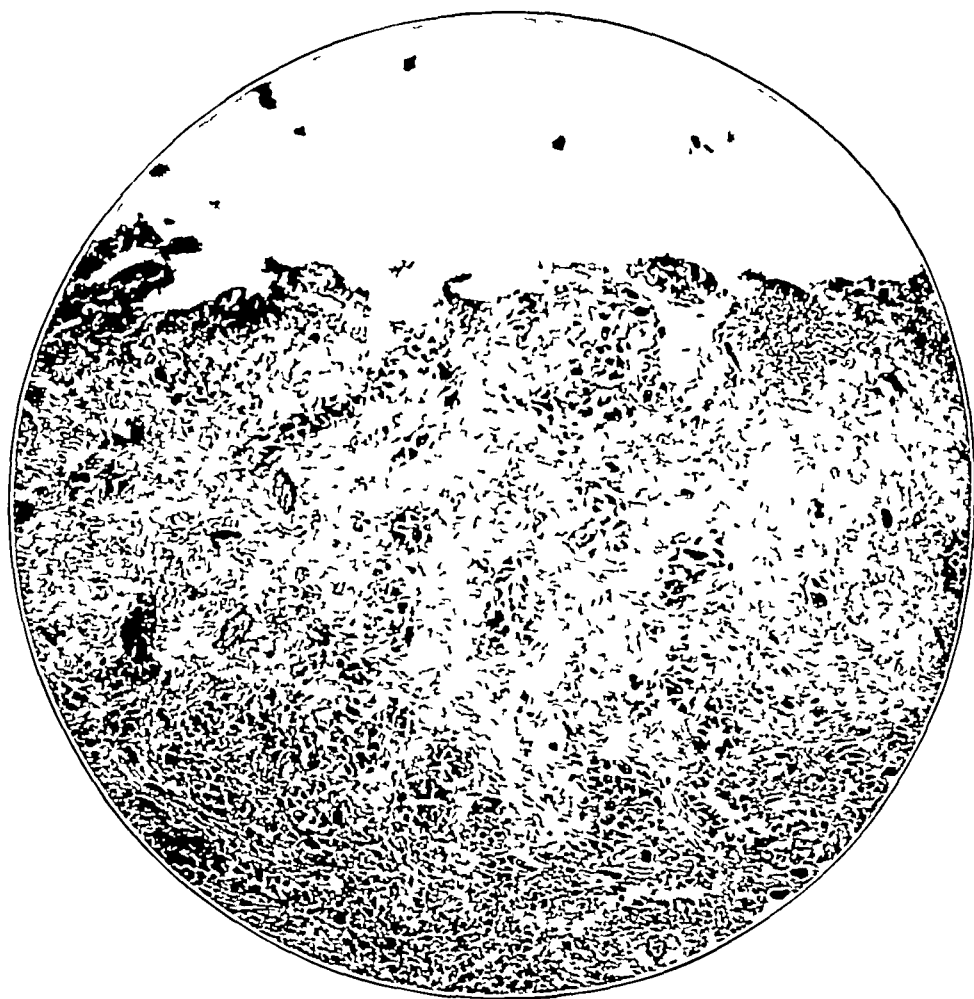


Fig 6 (case 6) —Common bile duct, showing hypertrophied villi and neoplastic proliferation of tumor cells on the surface with permeation of the wall and deeper tissue  $\times 50$

after partial dissection of the specimen. A cross section through the point of constriction revealed a triangular, firm, nodular lesion 1 cm on a side, embedded in the wall of the duct and in a portion of the underlying pancreas. The pancreas elsewhere showed extensive fatty infiltration and small areas of pancreatic necrosis. Proximal to the constriction the bile ducts were markedly dilated, the cystic duct readily admitting the passage of a probe. The fundus of the gallbladder was torn away, and the portion of the wall remaining was continuous with the large encysted area broken into as described. This cavity was walled in by the posterior surface



of the liver, the anterior wall of the colon, portions of the pancreas and duodenum and dense surrounding adhesions. No gallstones were found.

The liver was bile stained, soft, cystic and mottled with dark green areas intermingled with yellowish ones. On section of the liver little bile was found in the ducts, and there was a moderate increase in connective tissue. Apparently most of the bile had entered the cyst which enclosed the ruptured gallbladder.

The duodenum and the first portion of the jejunum contained a small amount of dark granular fluid. The feces were clay colored. Several lymph nodes about the common bile duct and pancreas were enlarged, soft and pigmented.

Microscopically the entire wall of the common bile duct at the point of obstruction and the underlying pancreas were involved by tumor growth over a triangular area measuring 1 cm on a side. On the surface of the duct the villi were hypertrophied owing to the presence of atypical epithelial cells (fig 6). The hypertrophied villi were separated by deep fissures. Elsewhere on the surface the epithelium was autolyzed. The tumor cells were essentially columnar, but some appeared round and elongated. Their nuclei were relatively large, hyperchromatic and irregular but rarely multiple, none were observed in mitosis. The cytoplasm was acidophilic and frequently showed one or more large vacuoles containing stringy mucin. The tumor cells were arranged chiefly in the form of acini of various sizes, many of them relatively large, or as clumps and strands. The stroma was abundant and contained a few inflammatory foci. Pancreatic permeation occurred chiefly in the interstitial tissue, with consequent atrophy of the parenchyma and perilobular fibrosis.

Small metastatic deposits were present in the cortical sinuses and afferent lymphatic vessels of one of the regional lymph nodes. The gallbladder was markedly thickened and fibrotic, with atrophy of the musculature and a diffuse inflammatory cell reaction, the epithelial lining was autolyzed. At the fundus, along the line of rupture, there was a wide zone of necrosis extending through the entire wall of the gallbladder, causing fragmentation and wide separation of tissue fibers, between which there was a deposit of brown pigment. The liver showed autolysis, marked biliary pigmentation, moderate fibrosis and inflammatory cell infiltration in the portal areas. Several small abscesses were present in the parenchyma. The kidneys showed marked biliary pigmentation. Siderotic nodules (Gamma-Gandy bodies) were present beneath the capsule of the spleen.

#### AGE AND SEX INCIDENCE

Twelve patients were men varying in age from 48 to 76 years, with an average of 60, and 9 were women varying in age from 42 to 76 years, with an average age of 60.

It was impossible to estimate accurately the incidence of proved primary carcinoma of the common bile duct exclusive of the ampulla of Vater and the duodenum, which of course are frequently invaded secondarily by tumors of the common duct. Many of the neoplasms considered in a previous communication on primary carcinoma of the peripapillary portion of the duodenum (Lieber, Stewart and Lund) may actually have arisen from the lower portion of the common bile duct. However as was set forth in that publication it was not possible absolutely to eliminate their origin from neighboring structures such

as the pancreatic duct, the ampulla of Vater or the duodenal mucous membrane covering the papilla of Vater. Therefore, the true incidence of primary carcinoma of the common bile duct must remain in doubt pending publication of statistical data which rest on carefully worked up material. The new case reported here occurred among 3,526 autopsies performed at the Jefferson Hospital (0.028 per cent of all autopsies).

#### MORBID ANATOMY

The location of the neoplasm could be accurately determined in 17 cases. In 7 it was localized in the lower end of the common bile duct, and in the remaining 10 the incidence was equally divided between the middle and upper segments, the exact situation of tumor in the other cases was not stated. However, it was perfectly clear that in all 21 cases there was complete absence of neoplastic involvement of the ampulla of Vater and the duodenal mucous membrane below and of the hepatic and cystic ducts above. The neoplasm formed a localized growth in 12 cases, varying in size from a few millimeters to the size of a pea, a cherry seed or a walnut, the largest growth being the size of a hen's egg. The tumors were soft, they were gray, yellow or white, with a granular papillary surface. In 1 case, 8 to 10 cm. of the common bile duct was involved by multiple soft, vegetating nodules between which the mucosa was thickened and hyperemic but not ulcerated. In 9 cases the neoplasm formed a diffuse, firm stenosing growth, granular and vegetating on the surface. There was ulceration in 6 cases, the ulcer being microscopic in 2, while in another it eroded deeply the wall of the bile duct into the head of the pancreas. With both the local and the diffuse types the wall of the duct was usually thickened as much as 1 cm.

Occlusion of the duct was complete in 11 cases, in the remainder no statement regarding the degree of obstruction was made. Proximal to the obstruction, the biliary ducts were maximally dilated.

Extension or metastases or both occurred in 11 cases, as follows: in the liver (6 cases), in the regional lymph nodes (5 cases), in the lungs (3 cases), and in the gallbladder (1 case). In 1 case, metastatic deposits were confined to a single lymph node above the left clavicle. In several cases only one or two regional lymph nodes contained metastatic deposits. The secondary growths in the liver were frequently multiple, but in 1 case there was an enormous solitary mass replacing a large portion of the organ. Extension of the primary process into the pancreas occurred in 4 cases, in 3 of which metastases were not present elsewhere. The infiltrating lesions were small in all instances, replacing a portion of the immediately underlying pancreas and invading vessels and nerves in 3 cases, while in the fourth an ulcerative lesion in the common duct also extended deeply into this organ.

The features of biliary stasis were present in all cases in which the liver was described, and some degree of cirrhosis was also present in 5 cases. In all but a single instance (to be noted) the gallbladder was distended or was not described. The contents of the gallbladder were clear and colorless in 6 cases and green, tarry and purulent in 1 case each. Biliary calculi were present in the gallbladder in 6 cases, in 1 of which the common bile duct also harbored a calculus. Marked cholecystitis was noted in 2 cases, and in 2 others the wall of the gallbladder was thickened. In our case in which the gallbladder had ruptured, the fundus was torn away, and what remained of the wall of the viscus was continuous with a large encysted area walled in by dense adhesions to the posterior surface of the liver, the anterior wall of the colon and portions of the pancreas and the duodenum. A considerable quantity of dark green granular fluid was contained in the cyst, with little bile remaining in the intrahepatic biliary passages. The pancreas, aside from neoplastic infiltration in 4 cases, showed relatively little change. There was slight pancreatic fibrosis in 4 cases and areas of fat necrosis in another. Obstruction of the pancreatic ducts was not described in any case in this series.

Peritoneal effusions occurred in 6 cases, the fluid being icteric in 4 and hemorrhagic in 2, in 1 of which the effusion followed laparotomy. A total of approximately 30 liters of icteric fluid was drained off by paracentesis on three occasions from a patient with continuous jaundice of eight month's duration. Pericholecystic adhesions were present in 7 cases (to the primary tumor, the duodenum, the stomach, the colon, the inferior and posterior surfaces of the liver and the anterior abdominal wall).

#### HISTOLOGIC PICTURE

The tumors in all but 1 of the cases in this series were glandular carcinomas, the exception being a squamous cell carcinoma (Cabot, case 16261). In 1 case carcinoma simplex was designated. Acini were present in the remainder and tended to uniformity in size, although some were anastomotic, with papillary spurs in 1 instance. Many atypical cells grew in the form of clumps or strands. The cells were essentially cylindric, columnar or cuboidal but varied considerably in size, shape and staining in many cases, pleomorphism being a marked feature in 3. Mitotic figures were observed in a single case, and multiple nuclei were noted in 2 others. The cells were generally well preserved, and little necrosis was evident. There was usually an abundant stroma, which was sparse in only a single instance.

The zone of malignant transformation as described in a few cases consisted of atypical epithelial cells several layers thick, eventuating in

the development of granular papillomatous formations or a solitary excrescence on the surface of the common duct. Chappet stated that the cancer in his case arose from the depths of the mucosa in the form of large alveoli which grew toward the lumen of the duct, the other layers of the duct were invaded with comparatively few cylindricocuboidal new formations in the submucosa. Devic and Gallavardin's case illustrates a tendency for the neoplasm to remain localized to the duct, which was thickened, ulcerated and lined by epithelial vegetations sharply separated, however, from the underlying pancreas by a thick band of connective tissue.

#### CLINICAL FEATURES

The clinical features of carcinoma of the extrahepatic bile ducts are based on a consideration of 104 cases, as follows: 35 cases of tumor primary in the hepatic duct, 48 of tumor primary at the confluence of the hepatic, cystic and common bile ducts, and 21 of tumor primary in the common bile duct. Since the symptoms and physical findings did not vary significantly with the point of involvement, this phase of the study is dealt with under one heading. Any clinical deviations dependent on the situation of the neoplasm as outlined in the section on morbid anatomy are indicated.

*Onset*—The onset was acute in 92 cases and gradual in 12. The symptoms occurring with the acute onset were jaundice (51 cases), pain (37 cases), pruritus (15 cases), loss of weight and strength (13 cases), vomiting (11 cases), anorexia (10 cases), fever (9 cases), diarrhea (7 cases), constipation (6 cases), nausea (5 cases) and (infrequently) chills, a sense of weight or pressure in the abdomen, flatulency and belching. Symptoms occurring after the onset were loss of weight and strength (48 cases), jaundice (41 cases), pruritus (19 cases), fever (13 cases), anorexia (12 cases), diarrhea (12 cases), pain (10 cases), constipation (9 cases), abdominal distention (5 cases), nausea (5 cases), vomiting (4 cases) and (infrequently) chills, a sense of weight or pressure in the abdomen, flatulency and belching.

Symptoms coinciding with the gradual onset were anorexia (6 cases), loss of weight and strength (5 cases), pain (4 cases), a sense of weight or pressure in the abdomen (3 cases), indefinite abdominal symptoms (3 cases), diarrhea (3 cases), nausea (2 cases), and vomiting and fever (1 case each). Later symptoms were jaundice (12 cases), vomiting (7 cases), loss of weight and strength (4 cases), pain (4 cases), fever (4 cases) and nausea, anorexia, chills and constipation (1 case each).

A history of an antecedent illness was elicited in 11 cases in which the onset was acute and in 1 case in which it was gradual. In the last-mentioned case long periods of pain and diarrhea antedated the gradual

onset by two years. In the first-mentioned group, variably brief attacks of pain, either single or multiple, were noted in 7 cases and preceded the onset of the present condition by one to five years. Of the remaining 4 cases, there were distention and discomfort after meals for five years in 1, long periods of diarrhea in 1, protracted, alternating diarrhea and constipation in 1 and pulmonary tuberculosis of two years' standing in the fourth.

*Jaundice*—This sign was present in all patients at some time during the course of the illness. Jaundice occurred at the onset in 51 cases and later in 53. With carcinoma of the hepatic and common bile ducts jaundice occurred equally early and late, but with carcinoma of the confluence of the three ducts a majority of patients exhibited jaundice later, in about the proportion of 5 to 3. In the group of cases in which jaundice occurred later the interval from the first appearance of symptoms to the onset of jaundice varied from a few days to eighteen months, averaging one and a half to two months except in the group with cancer of the hepatic duct, in which the average was about three months.

There was a single attack of jaundice in 90 cases, and, although variations in intensity occurred in all but 10 of these, an icteric tint was always present unless operation was resorted to. In Bret and Dufourt's case icterus was present without appreciable variation in intensity for eleven months. The duration of jaundice in 83 of the 90 cases varied from a few days to twenty-three months, averaging about three and one-half months. Jaundice was present for less than a month in 13 cases, for one month in 14, for two months in 13, for three months in 8, for four months in 11, for five months in 6, for six to twelve months in 17 and for twenty-three months in 1. There were two attacks of jaundice in 5 cases, and in the remainder the number of attacks was not stated. In the group with multiple attacks the duration of jaundice varied from a few days to five months, and the interval between attacks, from one week to one month. The sum of the duration of each individual attack of jaundice plus the interval between in 9 cases of this group varied from four to eighteen months, giving an average total duration of eight and one-half months.

Jaundice occurred as the sole sign in 13 cases and in association with loss of weight and strength only in 14, with diarrhea only in 4, and with fever only in 1. The relation of jaundice to the other commonly occurring symptoms is of interest. Jaundice was preceded by pain in 32 cases, by nausea or vomiting or both in 16, by anorexia in 14, by loss of weight and strength in 10 and by fever, sometimes with chills, in 5. Jaundice occurred simultaneously with pain in 10 cases, with loss

of weight and strength in 8, with nausea or vomiting or both in 5, with fever in 5 and with anorexia in 5. The appearance of jaundice was followed by loss of weight and strength in 52 cases, by fever in 17, by anorexia in 9, by pain in 13 and by nausea or vomiting or both in 6.

*Pain*—Pain was present in 55 cases, absent in 24 and not mentioned in the remainder. It occurred with the onset of the condition in 41 cases and later in 14. Pain was localized in the epigastrium or the right side of the hypochondrium or both in 36 cases, and in the back or the lumbar region in 2, in 1 case each it was present diffusely over the abdomen, in the left side of the abdomen and in the right flank. Pain radiated to the back in 5 cases, to the shoulders or the midscapular region in 3 and down both arms in 1. In another case, pain commenced in the left shoulder and radiated to the midthorax, the left side of the hypochondrium, the epigastrium and finally the right side of the hypochondrium. Pain was described as severe in 14 cases, colicky or cramp-like in 5, dull in 8 and vague in 3. It was intermittent in 24 cases and unremitting terminally in 5. A relation between food and pain existed in only 5 cases, of these, pain, heaviness or a sensation of pressure followed ingestion of food in all, continuing all night in 1. Nocturnal pain was a feature in an additional case. In another case a sensation of pressure in the epigastrium before meals became accentuated after eating.

*Nausea and Vomiting*—Vomiting was present in 23 cases, absent in 25 and not mentioned in the remainder. Vomiting occurred with the onset in 12 cases and later in 11. Nausea was complained of in 4 cases in which vomiting was not a symptom. Vomiting was intermittent and was never a distressing symptom. It was related to food in only 1 case, in which it sometimes followed ingestion of coarse food.

Examination of aspirated gastric contents was made in 9 cases, in 1 of which the material was reported as normal. In the others free hydrochloric acid was absent in 6 cases, reported as 13 in one and not mentioned in another. The total acidity in 6 cases varied from 10 to 31, with an average of 19. Lactic acid was present in 4 cases and absent in 2. Occult blood was present in 1 case. Duodenal drainage was performed in 5 cases. In Pangaro's case of carcinoma of the common bile duct without involvement of the duct of Wirsung, the duodenal fluid was clear and acid and contained bile but no pancreatic ferments. In Romano and Rey's case, in which bilirubin and pancreatic ferments were not found, autopsy revealed a carcinoma of the confluence of the bile ducts, but no mention was made of the pancreatic ducts. In Perez Fontana, Anastasia and Castro's case of carcinoma of the hepatic duct, repeated duodenal drainages were performed, and the fluid obtained

was always colorless. In Quenu and Gasne's case of carcinoma of the confluence of the bile ducts, the duodenal fluid on two occasions was slightly alkaline and contained bile pigments and a few pus cells but no blood. In our case 6, bile was absent from the duodenal contents.

*Diarrhea and Constipation*—Diarrhea occurred early in 10 cases and late in 12, while constipation occurred early in 6 and late in 9. Alternating diarrhea and constipation were manifested in 3 cases.

The stools were colorless, gray or clay colored in 56 cases, light brown in 1, slightly bile stained in another and not described in the remainder. In 2 cases the stools varied at times from normal to colorless. Blood was detected in 9 stools examined and absent in 6. Bile was present intermittently in 3 cases. The stools were occasionally fetid and contained an excess of fat in 8 cases.

#### PHYSICAL EXAMINATION

Abdominal masses representing the primary growth were not detected clinically in any case in this series. The liver was enlarged in 71 cases, in 3 of which it was nodular, it was not enlarged in 8 cases. The gallbladder was palpable in 27 cases and not palpable in 19. Abdominal tenderness was elicited in 26 cases, with associated rigidity in 3. Abdominal distention developed in 11 cases, usually late, and evidences of ascites were recorded in 8 cases. The spleen was enlarged and tender in 3 cases. In 1 case there was palpable enlargement of a lymph node in the left supraclavicular fossa.

#### OTHER LABORATORY DATA

*Studies of the Blood*—Studies were made in 26 cases. A varying grade of anemia was present in 17, the red blood cells varying from 2,300,000 to 3,850,000 per cubic millimeter in 13 cases, with only 910,000 red cells and a 15 per cent concentration of hemoglobin in 1 case. The values for hemoglobin varied from 15 to 85 per cent in 10 cases, in 4 of which the color index was high (1.02, 1.05, 1.18 and 1.37). In 1 case the red blood cell count and the hemoglobin level were normal. Slight leukocytosis was present in 4 cases, and in 2 the white cell counts were 25,000 and 30,000 per cubic millimeter respectively. The bleeding and coagulation times were estimated in 11 cases. The bleeding time was normal in all, there was prolongation of the coagulation time from twelve to twenty minutes in 4 cases. The van den Bergh estimations on the blood serum varied from 6.4 to 3.4 mg per hundred cubic centimeters in 4 cases with an average of about 22 mg. The icterus index varied from 30 to 150 in 6 determinations with 92 as an average. In 3 patients so examined tests of hepatic function with bromsulphalein

showed varying impairment, with 40 to 100 per cent retention of the dye in thirty minutes (2 mg dose). The value for blood sugar was within normal limits in 11 cases and increased to 200 mg in 1 case. Retention of nitrogenous products in the blood occurred in 4 cases.

*Urinalysis*—During icteric phases the urine was deep amber, green or dark brown, and bile was detected in every case in which a test for it was performed. Albumin in traces was detected in 12 cases and in large amounts in another. The urine contained sugar in 7 cases, in 1 of which the patient was treated daily with intravenous injections of dextrose solution. Urobilin was present in the urine in 9 cases and absent in 3. Casts, red cells, leukocytes and albumin suggested severe renal impairment in a few cases.

*Roentgen Examination*—Roentgen studies were carried out in 22 cases. In 8 cases, a simple flat plate of the abdomen was made. In 7 cases, examination of the gastrointestinal tract after a barium sulfate meal was reported as revealing no abnormality except diverticulosis of the colon in 1 case and cecal stasis in another. Positive findings were recorded in 6 cases of carcinoma of the confluence of the bile ducts and in 1 case of carcinoma of the hepatic duct. A brief analysis of these cases follows.

In Cabot's case 21,122 there were a hernia of the stomach and a diverticulum of the duodenal loop in the region of the gallbladder, at autopsy, a small tumor 1 cm in length obstructed the common bile duct at the orifice of the cystic duct, and the roentgen picture was not accounted for by gross examination. In Lee and Totten's case 1 rapid emptying of the stomach and duodenum suggested extrinsic irritation, at autopsy, a stricture of the common duct extended from 1.5 cm above to 0.5 cm below the orifice of the cystic duct. In McLaughlin's case 2 the roentgenograms were interpreted as indicating malignant disease of the stomach, at autopsy, the stomach and duodenum appeared normal, but the hepatic and common bile ducts were involved by new growth. In Kurths's case, the right half of the diaphragm was immovable, and an extragastric tumor was suggested from the roentgen studies, autopsy revealed a nodule the size of a cherry seed obstructing the ducts at the confluence. In Wahl's case 5, partial stenosis of the pylorus due to adhesions to the gallbladder was suggested, but autopsy revealed that the stomach and intestines were normal and that there were no adhesions about the gallbladder, an indurated mass 2 to 3 cm in length involved the cystic, common hepatic and common bile ducts. In Prat's case 2, gaseous dilatation of the intestines and adhesions between the stomach and the liver were suggested, at laparotomy however, the stomach and intestines showed no visible change and there were no adhesions but



instead a firm, nodular, indurated mass at the confluence of the bile ducts. In our case 3 there was a filling defect of the gastric antrum, with irregularity of outline, displacement, fixation and retention. Autopsy disclosed a soft, white nodule the size of a walnut in the hepatic duct, which merged with a larger mass in the liver.

The gallbladder was visualized in 1 case and not visualized in 5. An enlarged aorta, several large gallstones and a calcareous lymph node in the upper part of the abdomen were noted in 1 case each.

#### DIAGNOSIS

A correct provisional diagnosis was made clinically in 20 cases in which neoplastic obstruction of the bile ducts was suspected. In 33 cases one or more of the following diagnoses were made, carcinoma of the head of the pancreas (17 cases), carcinoma of the stomach (5 cases), calculous obstruction of the common bile duct (5 cases), carcinoma of the liver (3 cases), hypertrophic cirrhosis of the liver (3 cases), and carcinoma of the duodenum, carcinoma of the gallbladder, carcinoma of the colon, carcinoma of the prostate with hepatic metastases, obstructive jaundice due to malignant tumor, obstructive jaundice of undetermined origin, hemochromatosis, cholecystitis, angiocholitis and obstruction of the common bile duct by a plug of mucus (1 case each).

A correct surgical diagnosis of carcinoma of the hepatic duct, carcinoma of the confluence of the hepatic, cystic and common bile ducts or carcinoma of the common bile duct was made in 18 of 50 cases in which celiotomy was done. In 6 of these cases the lesion was localized in the region of the porta hepatis, or hilus of the liver. In 5 cases the primary lesion was mistaken for a benign fibrous stricture. One of the following diagnoses was made in each of 7 cases: stone in the hepatic duct, stones in the common bile duct, calculous cholecystitis, an indefinite mass behind the duodenum obstructing the bile ducts, tumor in the region of the pancreas, carcinoma of the papilla of Vater and metastatic tumor in the liver and omentum.

#### TREATMENT

The treatment of primary carcinoma of the extrahepatic bile ducts has been symptomatic, palliative or directed toward total eradication. The operative procedures, surgical results and pathologic observations differ widely depending on the point of obstruction, hence the following group analysis is presented.

*Carcinoma of the Hepatic Duct*—Fourteen patients were treated symptomatically only, and 12 lived for two to twenty-three months after onset with an average of eight and eight-tenths months. In 2 cases the duration of illness was not recorded.

Celiotomy was performed in 21 cases, and the operative procedures and results are indicated in table 1. A summary of the surgical pathologic features of these cases follows. A lesion in the region of

TABLE 1—*Results in Cases of Carcinoma of the Hepatic Ducts in Which Operation Was Performed*

Year	Author	Operation	Result
1893	Hesper, case 2	6/25/92 exploratory operation	Patient died 3 days after first operation
		6/30/92 cholecystostomy	Patient died 6 days after second operation
1898	Schuehardt	6/6/98 exploratory operation	Patient died 2 months after first operation
		7/6/98 choledochotomy	Patient died 1 month after second operation
1902	Ingelrans	Cholecystostomy	Patient died 19 days after operation
1904	Porot	Exploratory operation	Patient died 7 days after operation
1906	Houssin	Cholecystostomy	Patient died 20 days after operation
1907	Lapointe, Raymond and Merle	Exploratory operation	Patient died 2 days after operation
1908	Adlercreutz	Drainage of hepatic duct	Patient died several hours after operation
1910	Gutowitz	Cholecystectomy	Patient died 6 days after operation
1918	Petrén Case 14	Drainage of hepatic duct	Patient died 1 month after operation
	Case 16	Cholecystectomy	Patient died 1 day after operation
1924	Wahl, case 4	Exploratory operation	Patient died 1 day after operation
1931	Boseo	Exploratory operation	Patient died several hours after operation
1932	Milles and Koucky	Dilatation of stricture, removal of biopsy specimen, hepaticoduodenostomy	Patient died 4 days after operation
1932	David Case 1	Cholecystectomy, drainage of hepatic duct	Patient died 8 days after operation
	Case 2	7/7/23 cholecystectomy, choledochostomy 2/7/29	Patient died 8 months after first operation patient died 39 days after second operation
1933	McLaughlin, case 4	Cholecystogastrotomy	Patient died 9 days after operation, uremia, hemorrhage
1934	Lampert and McFetridge	Cholecystostomy	Patient died 14 days after operation
1934	Pérez Fontana, Anastasia and Castro, case 1	Cholecystoenterostomy	Patient died 5 days after operation
1935	Hess and Faltitschek, case 2	Exploratory operation	Patient died 1 day after operation
1935	Walters and Olson	Excision, biopsy, insertion of 10 mg radium of 14 hours	Patient living 4½ months after first operation
		One month later, excision of metastatic tumor on back	Patient living 3½ months after second operation
1939	Stewart, Lieber and Morgan	Cholecystostomy	Patient died 1 day after operation

the biliary ducts was detected by external palpation in 16 cases. The process was interpreted as a chronic inflammatory stricture in 3 of these cases and as an indurated lymph node in 2, in 5 cases, the local indurated lesion was thought to be an embedded stone, but in each of these incision of the bile ducts revealed the neoplastic process. In 6 remaining cases the tumor was unrecognized until autopsy was performed. The surgical

pathologic picture of these cases is interesting. The primary growths were all localized and small, ranging from the size of a pea to that of a walnut. Metastases in the regional lymph nodes were present in 3 cases. Peritoneal effusions of icteric fluid occurred in 3 cases and of bloody fluid in 1. The liver was usually enlarged and jaundiced. The gallbladder was distended in 5 cases, with white bile in 1 and blood-stained fluid in another, it was normal in size or not distended in 4 cases, being filled with thick mucopurulent material in 2 and thin icteric fluid in another. The gallbladder was collapsed and empty in 4 cases and contracted in 3, in 1 of which it embraced a large stone, another was adherent to the duodenum. No mention of the size of the gallbladder was made in the other cases, although calculi were present in 2 of these, in 1 of which stones were also present in the cystic duct. Variability in size of the gallbladder in this group of cancers of the hepatic duct requires emphasis and is to be contrasted with the picture in cases of carcinomatous obstruction at or below the terminal orifice of the cystic duct. In these cases cholecystic distention regularly takes place unless the gallbladder was previously diseased.

The clinical state of the patient after operation was commented on in only 5 cases. In Schuchardt's case, exploratory celiotomy was first performed, followed by choledochotomy a month later, jaundice remained as intense as before, and pain continued unabated, although the feces regained a slightly brown color. In Petren's case 14, drainage of the hepatic duct was followed several days later by bile staining of the secretions, and bile appeared in the feces eighteen days later. In David's case 2, after cholecystectomy and drainage of the common bile duct, jaundice gradually declined but reappeared, associated with pain, six months later, at which time the hepatic duct was found obstructed by a firm, fibrous thickening the size of the tip of the thumb. In Lampert and McFetridge's case, a cholecystostomy was performed two weeks before death, which, of course, did not relieve the bile stasis, as this was due to obstruction higher in the hepatic duct, and therefore jaundice failed to abate. In McLaughlin's case 4, cholecystogastrostomy was performed. The patient became practically anuric on the eighth day, the little urine obtained showing a cloud of albumin and large granular casts. Chemical examination of the blood showed the value for urea nitrogen to be 80 mg and that for creatinine to be 2.45 mg per hundred cubic centimeters, these values rose to 97 mg and 3.06 mg respectively on the following day. The patient died on the tenth postoperative day, after passing dark blood by bowel and vomiting 1,000 cc of dark blood. This case is probably illustrative of the hepatorenal syndrome, which in certain instances, at least, appears to have a morphologic basis (Lieber and Stewart). The liver in this case showed diffuse fibrosis and

extreme acute degeneration also resembling that described by us for patients subjected to surgical procedures on the gallbladder (Stewart and Lieber)

There was an ultimate mortality rate of 100 per cent in this series of carcinoma of the hepatic ducts. The total survival period from onset to death varied from one week to twelve months, averaging six and forty-eight hundredths months. The average postoperative survival period was nine-tenths month. Fourteen patients died during the first fourteen postoperative days, and 1 each on the nineteenth and twentieth days. The exact postoperative duration of survival was not recorded in 1 case, in which, however, there were extensive metastases one month after operation. Survival periods of one, two and eight months respectively were recorded in each of 3 cases, and in another, despite metastases, the patient was still alive four and a half months after operation. Of the 21 cases just enumerated, 2 deserve special mention. David's case 2 is of interest because of an eight month period of postoperative survival. At the first celiotomy, although no lesion was encountered, the gallbladder was removed and the common bile duct drained, and these operations, curiously enough, were attended by disappearance of jaundice. With recurrence of symptoms, a second celiotomy was performed seven months later, at which time an obstruction was found in the hepatic duct. Again the common bile duct was simply drained. The patient died five weeks later, eight months after the first operation. Obviously the operative procedures instituted in this case can be considered as having had little or nothing to do with disappearance of symptoms or with prolonging the life of the patient. Spontaneous regression of symptoms occurs sometimes in patients with cancer of the bile duct who are not subjected to surgical procedures. Certainly nothing effective was done in the case just cited to relieve the obstruction causing jaundice. The disappearance of jaundice under these circumstances must, therefore, be regarded as purely coincidental. Walters and Olson's case is particularly interesting, for it was the only one in which complete eradication of the neoplasm was attempted. At celiotomy in their case the common bile duct was found dilated and filled with masses of mucoid material, which were removed. In the region of the bifurcation of the hepatic duct a papillary lesion was located, with a pedicle about 1.5 cm. in diameter. This soft tumor was broken up, only a small portion of pedicle being left attached to the wall of the duct. Two radium needles (5 mg. each) were then placed in the duct for fourteen hours, after which the common duct was closed over a T tube. One month later, a mass 7 by 5 cm. presented itself posteriorly between the ninth and eleventh ribs. This gradually increased in size, and at the end of three weeks it was incised and drained, yielding a pint of

gelatinous material. The mass recurred, and still another nodule, 3 cm in diameter, appeared in the abdominal wall. The patient was last seen four and a half months after the first operation, and no record of his subsequent fate was available.

A comparison of the average total survival periods of the surgically treated patients (six and forty-eight hundredths months) and those treated medically (eight and eight-tenths months) gives the latter a slightly more favorable margin. The high immediate postoperative mortality rate, amounting to about 76 per cent, is largely responsible for this difference. Thus the increase in life expectancy which was accomplished in a few instances by surgical methods is completely nullified by the high immediate postoperative mortality. The favorable results obtained in a few instances, however, encourage early diagnosis, early operation and more detailed study of cases. The tumors are small, and slowly growing and metastasize late. When they are situated low in the common hepatic duct, excision with reestablishment of biliary flow may be feasible. A tumor at the upper end of the common hepatic duct frequently involves one or both branches of the duct, sometimes with direct spread into the liver and the nearby structures. The difficulties of instituting any sort of effective treatment under these circumstances can readily be appreciated.

*Carcinoma of the Confluence of the Ducts*—Twenty-seven patients were treated medically, and 26 of these lived for from one to eight months after onset, averaging four and six-tenths months, in the other case the duration of survival was not stated.

Celiotomy was performed on 21 patients, and the operative procedures and results are indicated in table 2. A consideration of the surgical pathologic picture in these cases follows. The primary neoplasm was correctly detected by direct palpation through the open abdomen in most instances, in 2, however, a localized growth was mistaken for a biliary calculus, and in another a more diffuse lesion was regarded as a benign fibrous stricture. The primary neoplasm varied in size from that of a cherry to that of a hazelnut. Metastases were encountered in only 2 cases. The liver was regularly enlarged and jaundiced. The gallbladder was frequently distended with clear, colorless fluid. However, it was small and thin walled in 4 cases and atrophied and thickened in another, in the last-mentioned case it contained many stones and a small quantity of purulent fluid. Gallstones were present in the gallbladder in 3 cases and in the cystic duct in 1. The hepatic ducts proximal to the obstructing neoplasm were dilated frequently with clear, colorless fluid.

There was an ultimate mortality rate of 100 per cent in this group. Thirteen patients died during the first fourteen postoperative days, and 1 died one and one-half months after operation. Seven patients how-

ever, survived for three, four, six, eleven, twelve, seventeen and twenty-seven months respectively, averaging about eleven and five-tenths months after operation. Their cases deserve individual mention. At

TABLE 2—*Results in Cases of Carcinoma of the Confluence of the Hepatic, Cystic and Common Bile Ducts in Which Operation was Performed*

Year	Author	Operation	Result
1899	Brenner, case 1	8/24/98 partial cholecystectomy, cholecystostomy 9/30/98 cholecysto- enterostomy 11/7/98 choledoch- enterostomy	Patient died 3 months after first operation Patient died 1½ months after second opera- tion Patient died ? months after third operation
1901	Lecène and Pagniez, case 1	Exploratory operation	Patient died 1 day after operation
1902	Uliszewski, case 2	Cholecystostomy	Patient died 9 days after operation hemor- rhage
1902	Miodowski case 6	Cholecystoenter- ostomy	Patient died 7 days after operation
1903	Kehr	Resection, chole- cystectomy, hepati- coduodenostomy	Patient died 27 months after operation
1904	Donati	Cholecystostomy	Patient died 1½ months after operation
1905	Weber and Michels	10/7/04 exploratory operation 12/13/04 intrahepatic cholangiostomy	Patient died 4½ months after operation Patient died 2 months after second opera- tion
1908	Borelius, case 1	Exploratory operation	Patient died 4 days after operation
1911	Spindler	Resection, chole- cystectomy, recon- struction of common and hepatic ducts	Patient died 7 days after operation
1912	Lameris	11/23/07 resection cholecystectomy, drainage of hepatic duct 8/27/08 resection of recurrent lesion, partial excision of liver, drainage of hepatic duct	Patient died 17 months after first operation Patient died 8 months after second operation
1921	Pallin, case 4	Resection, hepatico- duodenostomy	Patient died 11 months after operation
1923	Prat case 2	Resection, hepatico- duodenostomy	Patient died several hours after operation
1928	Vander Veer and Nellus	Cholecystostomy	Patient died 4 days after operation
1928	Pliverić	Resection	Patient died 10 days after operation
1929	Carnot	Choledochotomy, biopsy	Patient died 3 days after operation
1931	Mondor	Hepaticogastros- tomy	Patient died 6 months after operation
1933	McLaughlin, case 3	Exploratory operation	Patient died 5 days after operation
1934	Lee and Totten, case 1	Dilatation of stric- ture and catheter inserted to restore lumen of hepatic and common bile ducts	Patient died 7 days after operation hemor- rhage
1935	Romano and Rey, case 1	Cholecystostomy	Patient died ? days after operation
1936	Quénu and Gasne	Resection, hepatico- duodenostomy	Patient died 12 months after operation
1937	Cabot, case 22492	Removal of biopsy specimen	Patient died 4 days after operation

celiotomy in Kehr's case a round, hard hazelnut-sized tumor was palpated at the bifurcation of the cystic and hepatic ducts, and a stone of about equal size was embedded in the cystic duct. The gallbladder,

the cystic duct, 1.5 cm of the proximal portion of the common bile duct and 2 cm of the lower portion of the common hepatic duct were excised, and the stump of the last-mentioned structure was then implanted into the duodenum. No notes as to the immediate subsequent clinical course of the patient were recorded, but death twenty-seven months later was attributed to abscesses of the liver. At the first celiotomy in Lameris' case, a walnut-sized tumor at the confluence of the ducts was excised, and a cholecystectomy was performed, together with drainage of the hepatic duct. The symptoms gradually disappeared, and the patient regained his previous good health for nine months, after which, at the second celiotomy, a recurrent tumor the size of a hen's egg was found partly in the liver and partly in the hepatoduodenal ligament. To remove the tumor it was necessary to excise a portion (6 by 2.5 cm) of the right lobe of the liver. The jejunum was brought up and anastomosed to the hepatic wound, and a drain was inserted into the remnant of the hepatic duct. The patient was again free from symptoms for about five and one-half months and then complained of loss of weight and slight fever and died seventeen months after the first operation, eight months after the second operation. At autopsy there were metastases and numerous abscesses in both lobes of the liver. The jejunum when opened showed ten small openings on the mucosa, from which a rather large quantity of greenish yellow bile was expressed by applying pressure to the liver. Microscopically these openings proved to be newly formed biliary ducts from the liver which were functioning satisfactorily eight months after hepatointestinal anastomosis. In Quenu and Gasne's case, a hazelnut-sized tumor at the confluence of the ducts was excised, and the hepatic duct was implanted in the duodenum. The feces acquired bile staining in twenty days, and icterus finally disappeared completely. No further record of the patient's condition was made until death, twelve months after celiotomy, and unfortunately no autopsy was performed. In Pallin's case a tumor 2 cm long at the confluence of the ducts was excised, and the stump of the hepatic duct was anastomosed to the duodenum. The patient remained in good health for nine months, then epigastric pain developed, together with recurrent chills and fever, followed by increasing jaundice. Death occurred eleven months after celiotomy, and autopsy revealed suppurative cholangitis with multiple hepatic abscesses. Since no remains of the cancer were detected at autopsy, this patient might be regarded as potentially cured of the neoplasm, although death was due to its secondary effects. However the survival period of nine months was too short to make this a conclusive cure of cancer. Celiotomy in Mondor's case revealed an olive-sized mass at the confluence of the ducts, and the hepatic duct was anastomosed to the stomach. All symptoms gradually disappeared coincidentally with a gain of 10 Kg in weight in five months. The

patient then had increasing icterus, intermittent fever and digestive disturbances and died six months after surgical therapy was instituted. Autopsy showed that the stoma of the previous anastomosis was permeable but that the intrahepatic biliary ducts were filled with pus. It may be noted as indicating the slow progress of the disease that the tumor was not appreciably larger at this time than at first inspection and preserved the same general contour. In Weber and Michels' case, celiotomy on two occasions within two months failed to reveal the cause for jaundice which had persisted for three months. At the second operation a hole 3 cm deep was bored into the liver by an electrocautery, and a drainage tube was placed within it. Jaundice gradually disappeared, and there was a gain in weight, although occasional vomiting occurred. A month and a half later irregular fever, edema and slight purpura of the legs developed, which terminated fatally within two weeks. Autopsy showed that biliary obstruction was due to an infiltrating tumor confined to the confluence of the bile ducts. The fistulous opening produced at the second operation communicated with one of the intrahepatic biliary ducts. Tuberculous foci were widely distributed in the lungs, the spleen, the peritoneum, the omentum and the lymph nodes at the hilus of the liver. In Brenner's case a cherry-sized tumor was palpated near the duodenum. Seventy-three gallstones were removed from the gallbladder, a portion of which was excised, and a drain was inserted. At the second celiotomy, one and a half months later an abscess lying between the gallbladder and the liver was evacuated, and a cholecystoenterostomy was established. At the third celiotomy the cholecystoenterostomy was separated, and the dilated bile duct was implanted into the previous opening in the intestine. Death followed three months after the first operation, and autopsy revealed fibrinous peritonitis and metastases in the liver and regional lymph nodes.

These cases illustrate a number of interesting facts. Although no cure was effected by surgical therapy, the condition is not entirely hopeless. Any operation designed for drainage of the distended biliary tract by utilization of the extrahepatic biliary ducts below the highest point of the neoplasm would of course be ineffective in obviating bile stasis. The higher the neoplasm extends toward the liver, the more difficult surgical drainage becomes. In this connection, the procedures of anastomosing the jejunum to the incised liver as in Lameris' case and of puncturing the liver and draining the intrahepatic biliary ducts as in Weber and Michels' case are no doubt justifiable on occasion. Of the 6 patients who survived four months or longer after operation, death was apparently due to ascending biliary tract infection in 5, no information on this feature was available in Quénu and Gasne's case, for no autopsy was performed. The case of Lameris and that of Mondor also serve to emphasize the slow growth of these neoplasms, for in the latter no change



in size was detected after an interval of six months, and in the former the neoplasm increased only from the size of a walnut to that of a hen's egg during nine months. Metastases were noted in Brenner's case five months after the onset and (incidentally) in Borehus' case six months after onset.

Generally speaking, then, symptoms appear early, the neoplasm is slow growing and metastases occur late. The gravest concern is the high immediate postoperative mortality (66.6 per cent). Of significance is the fact that these patients were ill for about four months on the average before operation as contrasted with two months for those patients who survived for three months or longer after operation. Early

TABLE 3—*Results in Cases of Carcinoma of the Common Bile Duct in Which Operation Was Performed*

Year	Author	Operation	Result
1896	Griffon and Dartiques	Cholecystostomy	Patient died 7 days after operation
1902	Uliszewski, case 1	Resection of gall bladder cystic duct and common bile duct drainage of hepatic duct	Patient died 3 days after operation
1908	Borellus, case 2	Exploratory operation	Patient died 2 days after operation
1909	Morian, case 4	Resection cholecystoduodenostomy	Patient living and well 10 months after operation
1917	Petrén, case 20	Cholecystoenterostomy	Patient died 2 days after operation hemorrhage
	Case 22	Cholecystectomy drainage of hepatic duct	Patient died several hours after operation
1950	Shapiro and Litven dahl, case 10	Cholecystostomy	Patient died 7 days after operation hemorrhage
1935	Demel	Resection subserous cholecystectomy hepaticoduodenostomy anastomosis of cut ends of ducts	Patient died 7 months after operation

diagnosis and early operation while the patient's condition is not yet critical yield vastly more satisfactory results, according to these figures.

Although the surgeon has a limited field in which to work, in a number of the cases cited resection of the primary neoplasm followed by reestablishment of biliary flow by implantation of the hepatic duct into the gastrointestinal tract was satisfactorily accomplished. There was an immediate surgical mortality of 66.6 per cent. The total survival period from the onset to death in the surgically treated group averaged seven and sixteen hundredths months as compared with four and six-tenths months for the patients treated medically only.

*Carcinoma of the Common Bile Duct*—Thirteen patients were treated medically only and lived from one to eleven months after onset, averaging four and four-tenths months.

Surgical therapy was instituted in 8 cases and the operative procedures and results are indicated in table 3. The primary neoplasm was

detected by external palpation of the ducts at celiotomy in 4 cases and by attempting to pass a sound into the duct, which was obstructed in 1 case, in 3 cases the tumor was missed. The palpable growths varied from the size of a pea to that of a walnut, in 2 cases, metastatic deposits were present in the regional lymph nodes. The gallbladder was distended in 6 cases, containing clear, colorless fluid in 4 and tarlike fluid and stones in 1 each, no mention of this viscus was made in 2 cases.

No reference was made in any case to the general state of the patient during the postoperative period. Six patients died during the first seven postoperative days. The 2 patients who survived the immediate effects of operation are to be cited. At celiotomy in Demel's case, a pea-sized polypoid tumor in the proximal portion of the common bile duct was excised, together with the cystic duct and the gallbladder. A rubber tube was inserted through the papilla of Vater into the hepatic ducts, and severed ducts were anastomosed. Five weeks later the rubber tube was spontaneously evacuated. The patient died seven months after operation, but no autopsy was performed. In Morian's case, a tumor the size of a hazelnut in the distal part of the common bile duct was excised, and the gallbladder was anastomosed to the duodenum. The patient was still alive ten months after operation, although no "interim notes" were available. The duration of the disease from onset to death for the surgically treated patients averaged about two and two-tenths months in contrast to an average of four and four-tenths months for the patients treated medically only.

#### SUMMARY AND CONCLUSIONS

A clinical and pathologic study of carcinoma of the extrahepatic bile ducts is presented, based on 6 new cases and 98 cases satisfactorily reported in the literature, references to 211 additional cases reported under this title in the literature are listed.

One case was found in a series of 3,528 autopsies (0.028 per cent) and 5 cases in a series of 22,152 autopsies (0.022 per cent).

The average age was 59.3 years. Seventy-three patients were men, and 31 were women. In 3 cases, carcinoma of the hepatic duct occurred in comparatively young persons, aged respectively 29, 31 and 32 years.

The onset was acute in 88.5 per cent of cases and gradual in 11.5 per cent. The principal symptoms and signs, irrespective of the mode of onset, were jaundice, loss of weight and strength, pain, pruritus, anorexia, fever, vomiting, diarrhea, constipation and nausea. Other, less common symptoms were abdominal distention, chills, a sense of weight or pressure in the abdomen, flatulency and belching. Jaundice occurred in every case and pain in 52.9 per cent, and the two were associated at the onset in about 10 per cent. With carcinoma of the hepatic and common bile ducts, jaundice occurred equally early and late in the con-

dition, but with carcinoma of the confluence of the three ducts a majority of patients exhibited jaundice later, in about the proportion of 5 to 3. Fever, sometimes with chills, occurred in 26 per cent of cases, usually late. In no instance was a mass in the region of the primary tumor clinically palpable. The liver was palpably enlarged in 68 per cent of cases and the gallbladder in 26 per cent. A varying grade of anemia was the rule in the few cases in which the blood was examined. The gastric contents were examined in 9 cases and showed absence of free hydrochloric acid in 6 instances and the presence of lactic acid in 4, bile in 2 and blood in 1. The stools were usually clay colored or colorless, they were occasionally fetid, and they contained an excess of fat in 7 cases, blood was detected in 9 of 15 stools tested.

A correct provisional preoperative clinical diagnosis was made in about 20 per cent of cases. A correct surgical diagnosis was made in 36 per cent of cases in which celiotomy was done. Roentgen studies were of no direct value as an aid in clinical diagnosis.

The primary neoplasm in the group of cases of carcinoma of the hepatic duct (35 cases) formed a local tumor in 75 per cent. The growth averaged 2 cm. in diameter and consisted usually of an annular, constricting, grayish white lesion, with ulceration in 4 cases. A diffuse growth was present in 25 per cent of cases, with additional characteristics of widespread involvement and a tendency to extend into the liver in a wedge-shaped manner. Extension or metastases occurred in 48.5 per cent of cases, to the liver, lymph nodes, pancreas, gastrohepatic ligament and mediastinum. All the neoplasms were adenocarcinomas. In 1 case in this group there were multiple white infarcts of the liver, an extremely rare finding in the presence of biliary stasis in human beings. Variability in the size of the gallbladder in the group with carcinoma of the hepatic duct is to be contrasted with the findings in cases of carcinomatous obstruction at or below the terminal orifice of the cystic duct. Under the latter circumstances cholecystic distention regularly takes place unless the gallbladder has been previously thickened and atrophied by disease.

The neoplasms in the group with carcinoma of the confluence of the extrahepatic bile ducts (48 cases) formed a local tumor growth in 56.3 per cent of cases and a diffuse growth in 43.7 per cent. The local tumors were usually of the size of a hazelnut and formed either a single elevated projection above the mucous surface or an annular, constricting, gray, firm cartilaginous lesion. The diffuse type of neoplastic involvement was more extensive and appeared gray or white and fibrous or cartilaginous. Extension or metastases occurred in 45.8 per cent of cases, to the liver, lymph nodes, gallbladder, lung, peritoneum, pancreas, kidney and spleen. All the neoplasms were glandular carcinomas.

The neoplasms in the group with carcinoma of the common bile duct (21 cases) formed a local tumor growth in 57 per cent of cases and a diffuse growth in 43 per cent. The local tumors varied in size from a few millimeters to the size of a walnut and were soft, gray or white, with a granular or papillary surface. The diffuse growths were firm, stenosing, granular and vegetating on the surface. Extension or metastases occurred in 52.3 per cent of cases, to the liver, lymph nodes, lungs and gallbladder. The neoplasms were glandular carcinomas, with 1 exception, which was a squamous cell carcinoma.

The well known law for localization of cancer of the bile ducts at points of narrowing of the stream bed seems valid. Gallstones occurred in 20.2 per cent of cases.

An indubitably proved case of primary carcinoma of the cystic duct has not been found reported in the literature.

Surgical therapy was instituted in 50 cases. There was an ultimate mortality rate of 98 per cent, the fate of 1 patient remaining unrecorded. Included in this mortality rate figure is another case (Pallin) in which there was an eleven month postoperative survival period and in which no cancer could be demonstrated at autopsy. The immediate postoperative mortality rate was 68 per cent. Three patients with carcinoma of the hepatic duct survived for an average of three and six-tenths months after operation, and another was still living at the end of four and five-tenths months. The average total survival period for the 21 patients treated surgically in this group was six and forty-eight hundredths months as compared with eight and eight-tenths months for 12 of the 14 patients treated medically only. Seven patients with carcinoma of the confluence of the extrahepatic bile ducts survived for an average of eleven and five-tenths months after operation. The average total survival period for the 21 patients treated surgically in this group was seven and sixteen hundredths months, as compared with four and six-tenths months for 26 of the 27 patients treated medically only. One patient with carcinoma of the common bile duct survived for seven months after operation, and another was still living at the end of ten months. The average total survival period for 8 patients treated surgically in this group was about two and two-tenths months, as compared with four and four-tenths months for the 13 treated medically only. Early diagnosis is essential, and laparotomy performed early, when the patient's general condition is not yet critical, gives appreciably better results, according to the figures derived from this study. The effectiveness of this element is illustrated by the fact that the patients with carcinoma of the confluence of the extrahepatic bile ducts who succumbed to the immediate effects of operation were ill for an average of four months before operation, as contrasted with about two months for those patients who survived for three months or longer after operation.

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# METAPLASIA IN THE BREAST

ROBERT LEE OLIVER, M D

SAVANNAH, GA

A comprehensive examination of the literature has revealed no reference to the presence of pavement epithelium of primary origin in the mammary gland. Numerous reports, however, of metaplasia and its associated changes prove its frequency and include descriptions of its occurrence in several organs of the body, among which are the nose, frontal sinus, middle ear, lungs, esophagus, stomach, gall-bladder, pancreatic duct, renal pelvis, bladder, urethra, uterus and ovary. It is doubtful that metaplasia has actually been found in many of the reported cases, owing to the possibility of epithelium growing over from adjacent lesions of the skin or of the mucous membrane. Naturally, all fistulas warrant suspicion. The greatest offenders in the production of metaplasia have been reported as chronic inflammatory processes.

Consideration of a subject so complex as metaplasia and its associated processes demands brief mention of the striking figures in a literature which is muddled with a confusing terminology to which few authors have neglected to add.

Metaplastic processes in which there are simple changes in the configuration of the cells are commonly known under the nomenclature of von Hansemann and Borst<sup>1</sup> as histologic accommodation or variation. Other appellations of the same processes are Lubarsch's pseudo-metaplasia, Orth's<sup>1</sup> allomorpha and Ribbert's<sup>1</sup> retrogression.

Lubarsch<sup>2</sup> admirably described two processes. One is physiologic loss of differentiation through imperfect cell division. The other is pathologic loss of differentiation, which leads to destruction of cells by degeneration and atrophy in fully differentiated tissues. He termed these processes dedifferentiation. These changes are similar to those of Beneke's cataplasia and von Hansemann's anaplasia.

The term metaplasia, by which is meant the substitution of a specific cell or tissue for another differentiated cell or tissue, has been rejected

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From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University

1 Cited by Buchmann<sup>4</sup>

2 Lubarsch, O. The Question of Metaplasia and Its Significance in Tumors, *Arb a d path anat Abt. d k hyg Inst zu Posen R Virchow zur Feier*, 1901, pp 205-232, Metaplasia, *Centralbl f allg Path u path Anat* **17** 884-885, 1906, The Question of Metaplasia, *Verhandl d deutsch path Gesellsch* **10** 198-208, 1906-1907

by most authors in the strict sense of the word, as it is doubtful that such a direct change ever takes place. Transitional stages in the production of metaplastic processes in an indirect manner have been stressed by Ribbert and Schridde<sup>1</sup>. This view has been substantiated by Lubarsch,<sup>2</sup> Orth,<sup>1</sup> Gruber<sup>3</sup> and Buchmann<sup>4</sup> and is the more plausible course of development.

The researches of Stoeckenius,<sup>5</sup> Wenslaw<sup>6</sup> and Harms<sup>7</sup> show rather conclusively that all sorts of variations and malformations may arise from germinal tissue, and that under certain conditions fully developed epithelium may regain its embryonal aspect.

The striking relation between metaplasia and cancer formation, in that mechanical injuries and chronic inflammations are given as causes for both, has been noted by Buchmann,<sup>4</sup> who went further and stated that in many cases cancer is brought about by metaplasia of epithelium. Gruber<sup>3</sup> expressed the opinion that tumors with epithelium foreign to the site are suggestive of metaplasia but that it is more probable that they are due to malformations of embryonic tissue. Lubarsch<sup>2</sup> expressed the belief that metaplasia in cancer is rare.

In summarizing and presenting my own views it seems best to consider the possible mechanisms by which metaplasia and its associated processes may be brought about.

(a) In consideration of the derivation of metaplastic processes from a germinal cell or tissue, it must be understood that certain cells of the original germinal stock from which the specialized cell or tissue is derived may remain undifferentiated, though they are carried along with the differentiated cells in their development. Their presence in the specialized tissue is explained by this peculiar migration or displacement. The development of these immature cells with respect to the differentiated cells may proceed in a different direction.

(b) It can easily be seen that in the growth of cells or a tissue toward a certain specialization, there is a possibility that some cells may be retarded in their differentiation and may remain so, as do the completely undifferentiated cells in the specialized tissue. These cells, likewise, may develop along lines foreign to the site, thus presenting an appearance different from that of the tissue under consideration.

(c) The transformation of one specialized cell or tissue into another specialized cell or tissue of a different type is doubtful and rarely, if

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3 Gruber, G. B. Metaplasia, *München med Wchnschr* **61** 609-612, 1914.

4 Buchmann, E. The Present Status of the Metaplasia Question, *Cor-BI f schweiz Aerzte* **41** 270-283, 1911.

5 Stoeckenius, W. Data on Metaplasia, *Klin Wchnschr* **4** 1029-1033, 1925.

6 Wenslaw, A. Experimental Investigation on Metaplasia of the Pulmonary Epithelium, *Compt. rend Soc de biol* **106** 363-367, 1931.

7 Harms, W. Experimental Metaplasia in *Rana Fusca*, *Rös. Zool. Anz* **42** 49-55, 1913.

ever, occurs in a direct manner, although this possibility must be considered

In groups *b* and *c* the question of retrogression and variation arises. The partially differentiated cell or tissue as well as the completely differentiated cell or tissue may undergo transitional regressive changes, either in part or to the point of appearing as a completely undifferentiated cell. This process may be accounted for by the formation and nutrition of cells as set forth by Virchow<sup>8</sup>. The further development, then, along different lines in a direct manner may take place, although the whole process must be considered indirect, as transitional changes are necessary for the transformation of one given cell or tissue into another given cell or tissue which is specialized.

The later development along lines different from those followed by the specialized tissue is augmented in many instances by certain external forces, such as chronic irritation, mechanical stimuli and tumors, and by internal factors which have yet to be determined.

The mammary glands arise from a knoblike thickening of the ectoblast, occurring during the second month of fetal life. This thickening sinks into the underlying mesoblastic tissue, which undergoes proliferation and condensation and forms an investment for the growing epithelial mass. From this envelop the fibrous and muscular tissue of the areola and the nipple are derived, while the underlying mesoblast produces the connective tissue stroma. Solid epithelial sprouts grow out from the sides of the epidermal ingrowth and are the first anlagen of the true mammary gland, later becoming the excretory ducts. Subsequently, the central part of the ectoblastic plug undergoes degeneration and destruction, and what at first was an elevation becomes a depression. From the middle of the depressed area there appears, just prior to birth, an elevation which later becomes the nipple. Meanwhile, the epithelial ductal outgrowths penetrate the surrounding condensed stroma, increase in length, subdivide and acquire a lumen at their distal ends, due to desquamation of the central plug, thus giving rise to the system of ducts and lobules of immature gland tissue. With further development the surrounding stroma is broken up into the interlobular septum and fibrous framework. At birth the gland is represented by the lactiferous ducts with their ampullae, the smaller ducts and the immature alveoli. Temporary activity may occur in either sex a few days after birth, giving rise to the so-called witch's milk. The glands remain more or less stationary during childhood.

A brief review of the physiology of the breast and of the abnormalities associated with faulty cyclic processes, described by Oliver and

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<sup>8</sup> Virchow, R. About Metaplasia, Virchows Arch f path Anat 97 410-430 1884



Major<sup>9</sup> as cyclomastopathy, is presented with the hope of showing the major offending mechanism in the cases to be reported

Before the changes associated with puberty the breast consists chiefly of connective tissue in which there are a few ducts without definite lobular structure. The parenchyma is divided, however, into systems of ducts varying in number from ten to twenty the main duct of each

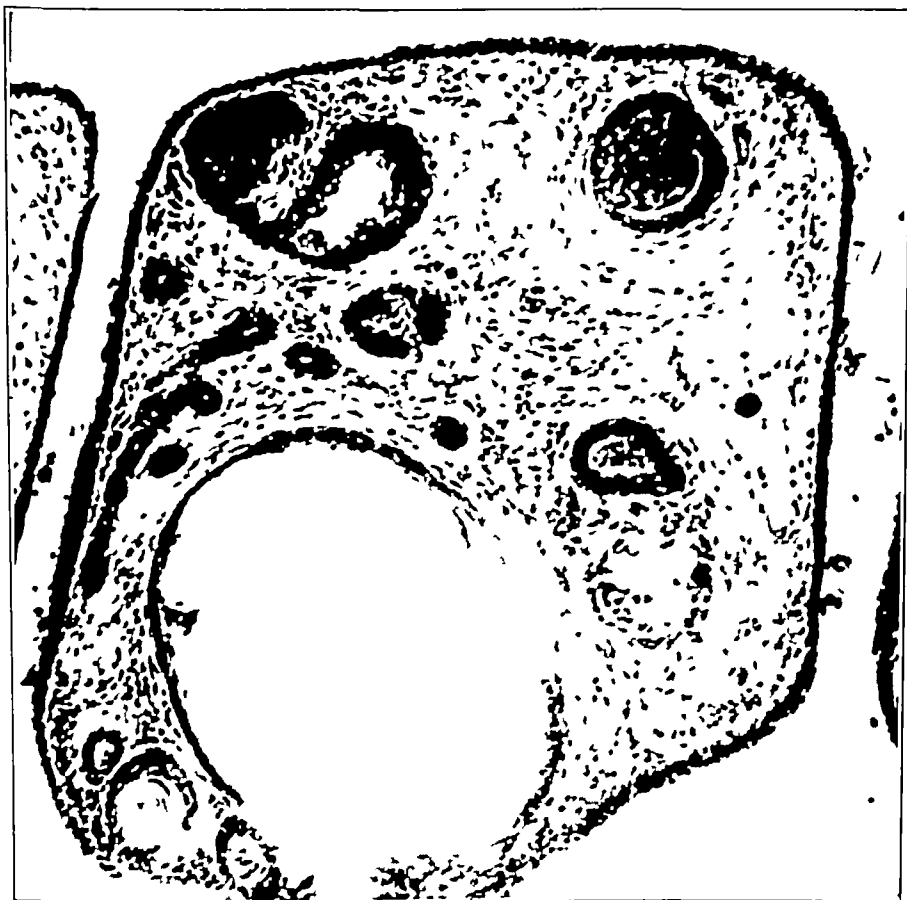


Fig 1 (case 1) —Photomicrograph showing variations in epithelial structure in a loose connective tissue stroma. This projection of tissue was found extending into a cyst or a dilated duct.

emerging individually at the nipple. The lobes are rather indistinctly separated by bands of fibrous tissue blending anteriorly with the skin and posteriorly with the chest wall.

<sup>9</sup> Oliver, R. L., and Major, R. C. Cyclomastopathy. A Physio-Pathological Conception of Some Benign Breast Tumors, with an Analysis of Four Hundred Cases, *Am J Cancer* **21** 1-85, 1934.

The changes at puberty occur as a result of hyperplasia of the periductal and interlobular connective tissue and of the ductal epithelium, which forms new branches. These changes are frequently accompanied with excessive proliferation of one or more of these elements, and local or diffuse hyperplasia results.

The hypertrophy of the breast during lactation consists of hyperplasia of the ductal and acinar epithelium and transient increase in the

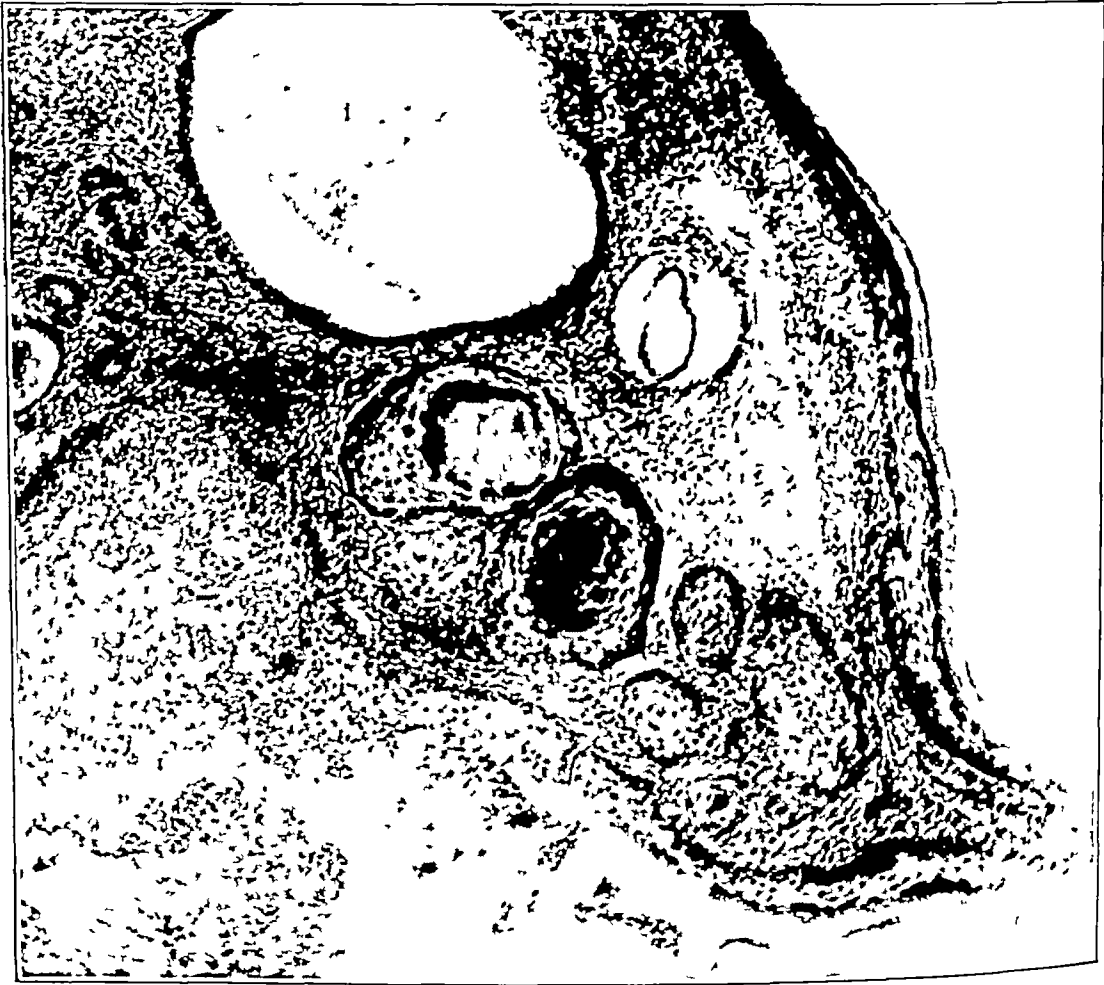


Fig 2 (case 1) —Photomicrograph showing a projection into a cystic cavity. The epithelium is definitely squamous, and some keratinization is seen. Pearly bodies are prominent.

intralobular connective tissue. Excessive growth of the parenchyma occurs in some instances but usually disappears with the ensuing involutionary process. Abnormal involution combined with exaggerations of proliferation of the periductal and periacinar connective tissue are as important in the formation of the cyclomastopathic processes as are the changes occurring at puberty.

There is some epithelial hyperplasia in the premenstrual phase of the menstrual cycle and hyperplasia of the connective tissue in the post-

menstrual phase The variety of combinations of epithelial and connective tissue elements presents evidence that there is some hyperplasia of both throughout different parts of the cycle, leading one to assume that the same lobule or lobules which respond to stimuli occurring in this cycle may involute with more than normal vigor, or vice versa It is clear that no hypertrophied nodule is left without being acted on and modified by additional stimuli



Fig 3 (case 2)—Photomicrograph showing the compressed capsule of the encapsulated tumor

It is obvious that the cyclic processes may show local nodules or diffuse involvement of one or both breasts These processes may present excessive proliferation of epithelial or connective tissue, or both, in response to growth stimuli Abnormal processes may be present as a result of faulty involution These proliferations or involutions, separately

or together, are aptly called cyclomastopathies. It is in these cyclomastopathic processes that the finding of epithelial metaplastic elements is reported.

#### REPORT OF CASES

CASE 1—A white married woman aged 50 complained of a tumor of the right breast of eight months' duration. On examination there was a large, fungating

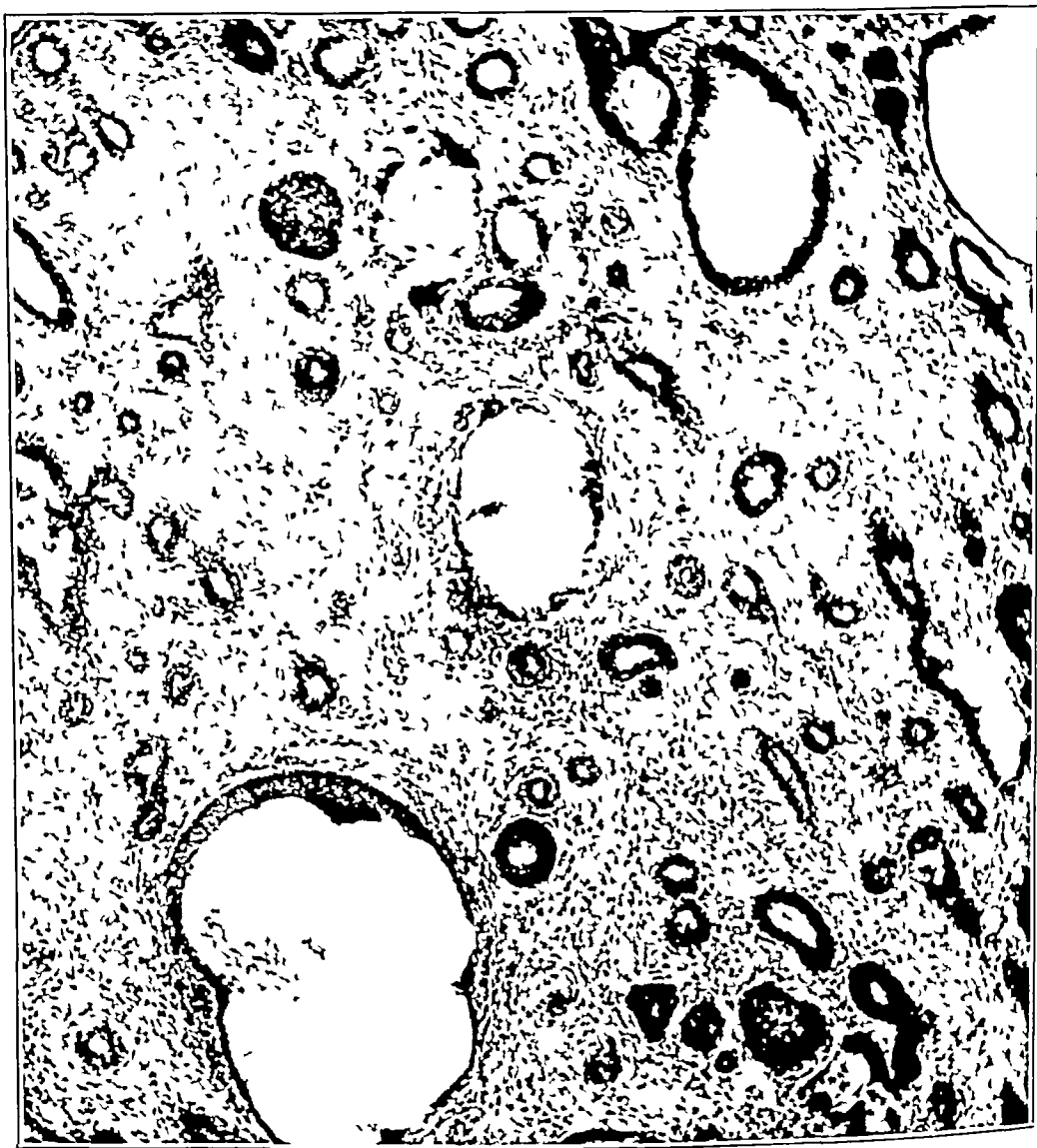


Fig. 4 (case 2) —Photomicrograph showing ducts and acini lined with a cuboidal or modified pavement type of cell.

circumscribed mass in the lower part of the breast. It was clinically malignant. The breast was amputated. The patient was followed for five years and was well at the end of that time.

The mass was encapsulated. Portions of the capsule contained some lobules of compressed tissue and fat. The mass was composed of a very dense stroma con-

taining many distorted structures lined by epithelium varying from squamous to columnar. The dense stroma appeared to be chiefly of interlobular origin, as few ducts or alveoli were arranged in groups. There was also intralobular hyperplasia, in that the intralobular markings were very indistinct, and the cells in general were of the same type. The ducts where they were enlarged, were considerably



Fig 5 (case 3) —Photomicrograph showing some acini filled with a transitional type of epithelium. Other dilated ducts are lined with columnar epithelium.

compressed. Some areas of hyalinization could be seen. The epithelial structures varied in size, and some cystic areas were noted. One of the larger cysts was lined with epithelium of pavement type with definite keratosis and hornification. Pearly bodies were distinctly seen in small groups just beneath the wall of this

cyst Transitions were noted between this type and the glandular type in the same section

CASE 2—A single white girl aged 16 had a slowly growing tumor of seven years' duration in the left breast. It was a lobular, hard, encapsulated, movable mass the size of one-half the breast and was clinically benign. It was excised. The ultimate result is unknown.

The mass was encapsulated and composed of a dense stroma containing many parenchymal structures. Some of the epithelial elements were dilated, and many huge papillae of hyperplastic connective tissue projected into the dilatations. The epithelial cells varied from glandular cells to modified pavement cells, some of which showed keratosis. There were no areas, however, which showed the extensive keratinization observed in case 1.

CASE 3—A white married woman aged 46 complained of a tumor of the right breast, with pain, of six months' duration. There was a history of rapid growth for the last two months. There was a firm, nodular, movable mass with areas of softening in the upper part of the breast, and it was clinically malignant. The complete operation for cancer was done, including dissection of the axilla. This patient remained well nine years after operation.

The mass was encapsulated. The tumor was composed of a rather dense stroma with many dilated epithelial structures of varying appearance. Some of the lining epithelium was of an orderly arrangement and composed of two definite layers, while other parts showed some piling up of epithelium with growth into the dilated cavities in the form of small papillae. This hyperplastic growth in some instances had an adenomatous appearance. There were a few definite cystic areas, as well as areas showing hyalinization. One of the larger cysts, in particular, was lined partly by pavement epithelium with hornification, which gradually merged into types of cuboidal to columnar arrangement.

#### COMMENT AND CONCLUSION

These cases are of importance in that the discovery of a pavement type of epithelium in the mammary gland is described in detail for the first time. It must be noted that this type of epithelium was deeply embedded in growths of cyclomastopathic origin and in no way could have been the result of the growing over of surface epithelium, which must be ruled out in all cases of suspected metaplastic processes. The presence of pavement epithelium in such a growth bears out the contention that mechanical stimuli may aid in inaugurating metaplastic processes. Whether embryonal displacement, simple retrogression into a kind of cell similar to the one from which it was derived or direct metaplasia is responsible for the change is a purely theoretic question. The fact remains that the change has taken place, and it is associated with changes similar to metaplasia and must be considered under this heading. The variation from the glandular to the pavement type of cell indicates strongly that the process is an indirect one, transitional changes being necessary for the transformation, as against the direct method, in which one specialized cell or tissue is changed into another specific cell or tissue without intermediate stages. No such abrupt change was seen in any of the sections.

# SERUM PROTEINS AND WOUND HEALING

HARRY KOSTER, M D  
AND  
ARTHUR SHAPIRO, M D  
BROOKLYN

Although many studies of serum proteins in the human being in the normal state and in various pathologic conditions have been published,<sup>1</sup> apparently no studies of serum protein concentration in relation to wound healing have been reported

We have studied the concentrations of total protein, albumin and globulin, the albumin-globulin ratio and the calculated protein oncotic pressure of the serum of 58 patients in the postoperative state whose wounds were carefully observed. In the cases of 17 who had hernioplasties with clean wounds (table 1) the determinations were done from one to ten days after operation (average four days). In the cases of 23 who had abdominal operations with clean wounds (table 2) the determinations were done from one to twenty-two days postoperatively (average eight days). In the cases of 16 who had abdominal wounds complicated by deep infections extending below the fascia (table 3) the determinations were done from one to twenty days postoperatively (average eleven days). In the cases of 8 who had clean wounds which disrupted during convalescence (table 4) the determinations were done from five to ten days postoperatively (average eight days).

All wounds were sutured with catgut in the deeper layers and with black silk in the skin. In the hernioplasty wounds the internal oblique muscle and the conjoined tendon (Bassini) or the internal oblique muscle, the conjoined tendon and the external oblique aponeurosis (Ferguson-Andrews) were sutured to the inguinal ligament with interrupted no. 2 chromic catgut. In the abdominal wounds the peritoneum was closed with continuous no. 2 plain catgut and the fascia with continuous no. 2 chromic catgut. In all the cases the black silk in the skin was a continuous suture.

The values for total serum protein were determined by aeration and titration after micro-Kjeldahl digestion.<sup>2</sup> The values for albumin were determined after precipitation of globulin with sodium sulfate.<sup>3</sup>

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From the Surgical Service of the Crown Heights Hospital

1 Bennhold, H., Kylin, E., and Rusznyák, S. *Die Eiweisskörper des Blutplasmas*, Dresden, Theodor Steinkopff, 1938

2 Sobel, A. E., Yuska, H., and Cohen, J. *J. Biol. Chem.* **118** 443, 1937

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TABLE 1—*Clean Hernioplasty Wounds*

Age of Patient	Operation	Days Between Operation and Determination	Protein, Gm per 100 Cc Serum	Albumin, Gm per 100 Cc Serum	Globulin, Gm per 100 Cc Serum	Albumin Globulin Ratio	Protein Oncotic Pressure, Cm H <sub>2</sub> O
52	Inguinal hernioplasty	2	8.40	5.53	2.87	1.92	41
56	Bilateral inguinal hernioplasty	1	8.30	5.33	2.97	1.80	41
43	Bilateral inguinal hernioplasty	3	6.85	4.69	2.16	2.17	30
41	Inguinal hernioplasty	10	7.13	3.90	3.23	1.25	27
65	Inguinal hernioplasty	2	6.75	4.42	2.33	1.90	28
33	Bilateral inguinal hernioplasty	2	6.88	4.05	2.23	2.08	30
17	Inguinal hernioplasty	4	7.25	4.89	2.36	2.07	33
47	Galli hernioplasty for recurrent inguinal hernia	5	7.57	4.77	2.80	1.70	32
24	Galli hernioplasty for recurrent inguinal hernia	2	7.68	4.39	3.29	1.33	31
52	Inguinal hernioplasty	2	7.75	4.76	2.99	1.59	32
42	Bilateral inguinal hernia	2	5.74	4.38	1.36	3.22	25
54	Inguinal strangulated hernia	8	5.87	3.64	2.23	1.63	22
48	Torex operation for undescended testicle, inguinal hernioplasty	2	5.88	3.46	2.42	1.43	21
43	Inguinal hernioplasty	3	5.95	4.21	1.74	2.42	25
21	Inguinal hernioplasty	9	6.75	3.46	3.29	1.05	23
48	Inguinal hernioplasty	1	6.15	4.58	1.57	2.92	27
41	Inguinal hernioplasty	8	6.09	3.84	2.25	1.70	23

TABLE 2—*Clean Abdominal Wounds*

Age of Patient	Diagnosis	Operation	Days Between Operation and Determination	Protein, Gm per 100 Cc Serum	Albumin, Gm per 100 Cc Serum	Globulin, Gm per 100 Cc Serum	Albumin Globulin Ratio	Protein Oncotic Pressure, Cm H <sub>2</sub> O
55	Cancer of stomach	Subtotal gastrectomy (Polya)	8	7.88	4.62	3.26	1.42	34
36	Recurrent cholecystitis and cholelithiasis with common duct obstruction	Laparotomy cholecystectomy, T tube drainage of common bile duct	14	6.38	4.61	1.77	2.60	28
42	Acute appendicitis	Appendectomy	10	6.74	4.58	2.16	2.12	27
32	Acute appendicitis	Appendectomy	9	6.05	3.85	2.20	1.75	20
30	Chronic appendicitis	Appendectomy	7	6.20	3.90	2.30	1.69	25
32	Acute appendicitis (gangrenous), intestinal obstruction	Appendectomy	19	6.69	4.12	2.57	1.60	26
32	Neuroma of appendix, early regional ileitis	Appendectomy removal of biopsy specimen	12	6.01	3.69	2.32	1.59	23
53	Fibroid uterus	Hysterectomy (supra cervical), appendectomy	5	6.17	4.05	2.12	1.90	25
40	Chronic cholelithiasis	Cholecystectomy, appendectomy	11	7.51	4.04	3.47	1.16	29
22	Acute gangrenous appendicitis	Appendectomy	10	6.53	4.33	2.20	1.97	27
18	Ruptured ovarian cyst	Appendectomy excision of cyst of ovary	9	6.59	4.74	1.85	2.56	30
29	Chronic appendicitis	Appendectomy	11	6.72	4.19	2.53	1.65	27
31	Chronic appendicitis, retroverted uterus	Appendectomy suspension of uterus plication of cecum	7	7.06	3.76	3.30	1.14	26
53	Chronic cholecystitis and cholelithiasis	Cholecystectomy appendectomy	1	7.40	4.02	3.38	1.19	30
39	Chronic appendicitis	Appendectomy	7	5.46	3.52	1.94	1.81	21
46	Scleroderma fibroid uterus chronic cholelithiasis	Supracervical hysterectomy, right salpingo-oophorectomy, appendectomy perineorrhaphy cholecystectomy	22	5.75	2.82	2.93	0.96	18
31	Cholelithiasis	Cholecystectomy	3	7.90	5.24	2.66	1.97	35
31	Duodenal ulcer	Subtotal gastrectomy (Polya)	1	7.82	5.13	2.69	1.90	35
46	Chronic cholecystitis, fibroid uterus	Cholecystectomy, supra cervical hysterectomy left salpingo-oophorectomy	6	6.72	4.12	2.60	1.53	27
38	Chronic cholelithiasis common duct obstruction	Cholecystectomy choledochostomy appendectomy	5	6.60	3.18	3.42	0.93	22
50	Bleeding duodenal ulcer	Subtotal gastrectomy (Polya)	10	7.60	3.54	4.06	0.87	26
49	Gastric ulcer	Subtotal gastrectomy (Polya)	1	5.95	3.84	2.11	1.82	23
40	Fibroid uterus chronic pelvic inflammatory disease	Supracervical hysterectomy bilateral salpingo-oophorectomy appendectomy perineorrhaphy	2	5.64	4.56	1.05	4.22	25



( $\text{Na}_2\text{SO}_4$ ) Oncotic pressure was estimated from empiric curves based on the observations of Wies and Peters <sup>4</sup>

The results are summarized in table 5

#### COMMENT

Harvey and Howes <sup>5</sup> noted an improvement in the rate of healing of gastric wounds in rats on a high protein diet Thompson, Ravdin and Frank <sup>6</sup> reported that after abdominal incision the wounds of 8 of 11 dogs previously fed a restricted diet and subjected to repeated plasmapheresis disrupted or failed to heal Although they gave no figures for serum protein, they stated, on the basis of previous studies, that the dogs had definite hypoproteinemia They suggested that this was a factor in the mechanism of wound disruption As a result of failure to produce disruption in 3 similarly prepared dogs which subsequently received lyophilized serum intravenously to raise the serum protein content, they suggested <sup>7</sup> that "retardation in healing of wounds associated with hypoproteinemia in dogs may be averted by restoration of the serum protein to normal levels immediately after operation"

However, the absence of data on the actual concentration of serum protein and its fractions in their experimental animals makes it difficult to evaluate their results or to attempt to apply them to human beings It is also worth noting that their observations were made on dogs suffering not merely from hypoproteinemia There is, indeed, little evidence that hypoproteinemia was the only metabolic disorder in their animals, maintained as they were on a restricted diet and subjected to repeated plasmapheresis

In our studies the values for the total proteins and fractions in the cases of patients with clean abdominal and hernial wounds are similar to the values reported in the literature for normal human beings <sup>1</sup> On the other hand, the average values for total protein, albumin and oncotic pressure in the cases of patients with deep infection and disruption were slightly but definitely lower than normal The value for globulin remained unchanged Whatever hypoproteinemia was present was therefore actually hypoalbuminemia (table 5)

4 Wies, C H., and Peters, J Osmotic Pressure of Proteins in Whole Serum, *J Clin. Investigation* **16** 93, 1937

5 Harvey, S C., and Howes, E L Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, *Ann Surg* **91** 641, 1930

6 Thompson, W D Ravdin, I S., and Frank, I L Effect of Hypoproteinemia on Wound Disruption, *Arch Surg* **36** 500 (March) 1938

7 Thompson, W D., Ravdin, I S., Rhoads, J E., and Frank, I L Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, *Arch Surg* **36** 509 (March) 1938

TABLE 3—*Deep Infection in Abdominal Wounds*

Age of Patient	Diagnosis	Operation	Days Between Operation and Defecation	Protein, Gm per 100 Cc Serum	Albumin, Gm per 100 Cc Serum	Globulin, Gm per 100 Cc Serum	Albumin Globulin Ratio	Protein Oncotic Pressure, Cm H <sub>2</sub> O	Comment
60	Acute gangrenous appendicitis with perforation, paralytic ileus, terminal hepatitis	Appendectomy, jejunostomy	9	5.22	3.44	1.78	1.93	19	Deep infection fascial slough on 7th day patient died with terminal hepatitis on 32d day
72	Acute gangrenous appendicitis with perforation and abscess	Appendectomy	9	0.05	3.30	2.09	1.25	21	Acute heart failure on the left on 2d day, acute parotitis on 8th day, foul bloody collection evacuated on 8th day, with extensive fascial slough, pneumonia on 33d day patient died on 39th day
81	Chronic cholecystitis	Cholecystectomy, appendectomy	18	0.51	3.37	3.14	1.07	23	Large collection evacuated from incision on 9th day wound opened on 10th day exposing extensive slough of all layers healed uneventfully after packing
55	Postoperative abdominal fistula with subhepatic abscess	Drainage of subhepatic abscess, cholecystostomy	12	5.22	2.86	2.36	1.21	17	Deep infection which drained pus around through and through sutures and continued to drain for several weeks
63	Acute gangrenous cholecystitis and cholelithiasis	Cholecystectomy	9	5.94	3.20	2.74	1.17	20	Deep collection evacuated on 8th day healed uneventfully after packing
42	Intestinal obstruction due to postoperative adhesions	Separation of adhesions Witzel enterostomy	3	5.09	3.37	2.32	1.45	20	Extensive gangrene of wound edges on 2d day patient given gas gangrene antitoxin wound healed after treatment with peroxide irrigations and packing

20	Acute appendicitis (gangrenous)	Appendectomy	7	5 55	3 64	1 91	1 90	21	Deep infection with slough of fascia evacuated on 5th day wound healed uneventfully after packing.
24	Acute gangrenous appendicitis	Appendectomy	8	5 70	3 04	2 71	1 12	19	Marked distention foul collection in wound evacuated on 8th day healed uneventfully after packing pneumonia with pleural effusion on 16th day patient discharged on 48th day
62	Chronic cholelithiasis common duct stone neoplasia lipomas	Cholecystectomy cholecystostomy nephropexy appendectomy excision of lipomas	20	5 61	3 44	2 17	1 57	21	Deep infections in all 3 wounds healed uneventfully after packing.
68	Lymphosarcoma of rectum	One stage abdominoperineal resection of rectum	10	4 79	2 39	2 40	0 99	14	Foul collection with fecal contamination evacuated from wound on 6th day edema of abdominal wall legs and scrotum on 6th day ulceration after coughing, spells on 11th day suppurative epididymitis on 15th day stormy course but wounds healed after packing and patient was discharged on the 30th day
30	Gangrenous Meckel's diverticulum	Appendectomy resection of Meckel's diverticulum	22	5 89	4 35	1 54	2 82	26	Deep purulent collection evacuated on 4th day wound healed uneventfully after packing
57	Acute gangrenous cholecystitis	Cholecystectomy appendectomy	11	6 70	4 32	2 44	1 77	23	Pneumonia on 6th day deep collection evacuated on 6th day wound healed uneventfully after packing patient discharged on 46th day
23	Acute appendicitis	Appendectomy	8	7 03	4 57	2 46	1 53	30	Foul collection of brownish fluid evacuated on the 7th day wound healed uneventfully after packing

TABLE 4—*Wound Disruption*

Age of Patient	Diagnosis	Operation	Days Between Operation and Disruption	Protein, Gm per 100 Cc Serum	Albumin, Gm per 100 Cc Serum	Globulin, Gm per 100 Cc Serum	Albumin Globulin Ratio	Protein Oncotic Pressure, Om H <sub>2</sub> O	Comment
22	Acute typhilitis	Exploratory laparotomy, appendectomy	7	4.96	3.30	1.66	1.99	18	Patient severely distended wound disruption on 8th day after operation packed and strapped acute intestinal obstruction on 11th day emergency enterostomy proximal to obstruction by kinked loop of bowel patient died on following day
61	Duodenal ulcer	Posterior gastroenterotomy, cholecystectomy	10	4.32	2.88	1.44	2.0	15	Wound disrupted on 10th day after operation wound clean packed and strapped, healed uneventfully
64	Chronic cholecystitis and cholelithiasis with common duct obstruction	Cholecystectomy, choledochostomy with T tube	5	5.92	3.64	2.28	1.60	22	Complete wound disruption on 9th day, resutured wound healed uneventfully except for slight separation at the upper angle 9 days after resuturing
47	Acute gangrenous cholecystitis	Cholecystectomy, appendectomy	7	5.73	3.37	2.36	1.43	21	Complete wound disruption on 6th day wound clean resutured uneventful healing
55	Chronic cholecystitis with stones in cystic duct	Cholecystectomy, exploratory duodenotomy	8	7.12	3.47	3.65	0.95	25	Complete wound disruption on 5th day wound clean resutured uneventful healing
56	Chronic appendicitis	Appendectomy, separation of adhesions	7	7.17	3.60	3.57	1.01	26	Complete wound disruption on 5th day, wound clean resutured uneventful healing patient had chronic cough
31	Acute cholecystitis and cholelithiasis	Cholecystectomy separation of adhesions	9	6.25	3.74	2.51	1.40	23	Complete wound disruption on 18th day with discharge of biliary collection from abdomen pneumonia on 6th day wound resutured with drain in upper angle uneventful healing

It can be seen from table 4 that among the patients with wound disruption the highest value for serum albumin was 3.74 Gm per hundred cubic centimeters. All 8 patients with disrupted wounds and 10 of the 13 patients with deep wound infections had serum albumin concentrations of less than 3.75 Gm per hundred cubic centimeters, whereas only 5 of the 23 patients with clean abdominal wounds and 3 of the 17 patients with clean hernioplasty wounds had concentrations below this level. In other words, 86 per cent of the patients with complicated wounds had serum albumin concentrations below 3.75 Gm per hundred cubic centimeters, whereas only 20 per cent of the patients with clean wounds had such low concentrations.

TABLE 5—*Postoperative Levels of Serum Protein Classified According to Condition of Wounds*

Classification	Protein, Gm per 100 Cc Serum	Albumin Gm per 100 Cc Serum	Globulin Gm per 100 Cc Serum	Albumin Globulin Ratio	Protein Oncotic Pressure Cm H <sub>2</sub> O
Clean hernia wounds	6.88 ± 0.18	4.41 ± 0.12	2.47 ± 0.12	1.89 ± 0.10	28.4 ± 0.1
Clean abdominal wounds	6.60 ± 0.12	4.10 ± 0.09	2.56 ± 0.11	1.76 ± 0.10	26.0 ± 0.7
Deep infection in abdominal wounds	5.54 ± 0.13	3.49 ± 0.10	2.36 ± 0.10	1.55 ± 0.12	21.5 ± 0.9
Disrupted abdominal wounds	6.08 ± 0.32	3.45 ± 0.07	2.63 ± 0.26	1.44 ± 0.12	21.9 ± 1.1

#### SUMMARY AND CONCLUSIONS

The concentrations of total protein, albumin and globulin and the calculated protein oncotic pressure of serum in the cases of 58 patients whose operative wounds were carefully observed are reported.

In general, patients who had deep infection or disruption of their wounds showed lower values for total protein and for oncotic pressure in their serum. This was due mainly to a diminution in the albumin fraction.

The occurrence of normal concentrations of serum protein and albumin in some patients with infected or disrupted wounds and relatively low concentrations in some with clean wounds implies that hypoproteinemia by itself is neither a necessary nor a sufficient condition for the development of wound infection or disruption. However, the similarity in the concentrations of total serum protein and serum albumin and in the serum protein oncotic pressures in the groups with deep infection and wound disruption suggests the idea that the poor nutritional state of which hypoproteinemia is a manifestation may favor both the development of deep infection and the disruption of clean wounds.

# FUCHS TEST FOR MALIGNANCY

C S ROBINSON, PH D

RAY EVERS, MD

AND

ALLEN TRUEX, BA

NASHVILLE, TENN

The test for malignancy which is the subject of the present paper was first described in 1926<sup>1</sup>. It has been the object of considerable attention in Europe since that time and has served as the basis for a number of immunologic investigations by its author and others. Clinical studies have been reported on more than 1,000 cases, with an accuracy of about 90 per cent. There appears to have been no work done on it in the United States.

Fuchs observed that washed fibrin from one species of animal was not digested by serum from the same species but was digested by serum from other species. This reaction appeared to be so specific that different breeds of the same animal, e g, rabbits,<sup>2</sup> could be distinguished from each other by means of it. He then investigated the reactions of pathologic blood and found that blood from patients suffering from various diseases, notably syphilis, tuberculosis<sup>3</sup> or malignant tumors, reacted toward blood from healthy subjects as though it were from another species of animal. Thus, the fibrin from the blood of a patient with cancer was digested by serum from a noncancerous person but not by that from another person with cancer, while serum from a subject with cancer digested the fibrin from a normal person, but did not affect fibrin from another subject with cancer. Similar results were secured with blood from patients with syphilis, tuberculosis and other

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From the Department of Biochemistry, Vanderbilt University School of Medicine

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1 Fuchs, H J (a) *Proteolytic Enzymes in Serum I*, *Biochem Ztschr* **170** 76, 1926, (b) *Proteolytic Enzymes in Serum II*, *ibid* **175** 185, 1926

2 (a) von Falkenhausen, M, Fuchs, H J, and Schubul, M. *The Differences in Sera of Various Stages of Metamorphosis of Anuren*, *Biochem Ztschr* **193** 269, 1928 (b) Fuchs, H J, and von Falkenhausen, M. *Proteolytic Ferments in Serum VI*, *ibid* **181** 438, 1927

3 (a) Fuchs, H J. *On Proteolytic Ferments in Serum IV*, *Biochem Ztschr* **178** 152, 1926 (b) Fuchs, H, von Falkenhausen, M, and Kowarzyk, H. *Specificity of Fibrin III*, *Ztschr f Immunitätsforsch u exper Therap* **80** 233 1933 (c) Fuchs<sup>1b</sup> and von Falkenhausen

diseases, so that false positive reactions were obtained unless precautions were taken to rule them out. It appeared that false negative reactions were rare, and hence the real value of the test lay in its ability to rule out malignancy of a tumor in doubtful cases.

In addition to the negative results (with no change in soluble nitrogen) and the positive results (with an increase in soluble nitrogen), Fuchs described a so-called "immune reaction," obtained in certain cases of infectious disease, in which there was a decrease in soluble nitrogen.<sup>4</sup>

Shortly after its publication, the work of Fuchs was subjected to critical examination by a number of workers. Wright and Wolf<sup>5</sup> studied the conditions necessary for its successful operation and reported results in 116 cases. In 45 cases of proved malignant tumor the results were positive, and no malignancy was proved in cases in which there were negative reactions. Surgical or radium therapy reversed the reaction, causing decreases in soluble nitrogen. Cadness and Wolf<sup>6</sup> obtained 18 positive reactions in 18 cases of proved malignant tumors. In 16 cases of benign disease they secured 5 positive reactions, 4 in cases of gastric ulcer and 1 in a case of nephritis. Yokota<sup>7</sup> and Van der Scheer<sup>8</sup> failed to confirm Fuchs's results, but their technic was imperfect.<sup>9</sup> Bernhard and Kohler<sup>10</sup> compared the Fuchs test with the lipase test, which they found to be unreliable. In 247 proved cases they reported 129 positive, 86 immune and 17 negative Fuchs reactions. In 164 cases of nonmalignant disease 9 reactions to the Fuchs test were positive, 7 were immune and 142 were negative. They found the site of the tumor to be without significance except that in cases of esophageal tumor false negative reactions were obtained. They claimed that precancerous conditions may be indicated by supposedly false positive reactions, which should always be viewed with concern. Jedlička and Weichherz.<sup>11</sup>

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4 Fuchs, H. J., and von Falkenhausen, M. A Chemically Measurable Toxin-Antitoxin Combination in Vitro, *Biochem Ztschr* **176** 92, 1926, The Behavior of Immune Sera and Immune Fibrin, *ibid* **178** 155, 1927.

5 Wright, M. W., and Wolf, C. G. L. The Serological Diagnosis of Cancer, *J. Cancer Research* **14** 370, 1930.

6 Cadness, B. H. E., and Wolf, C. G. L. Contribution to the Fuchs Reaction for the Serum Diagnosis of Carcinoma II, *Biochem Ztschr* **238** 287, 1931.

7 Yokota, K. The Question of the Occurrence of Proteolytic Enzymes in Serum, *Biochem Ztschr* **232** 58, 1931.

8 Van der Scheer, J. On the Action of Serum on the Fibrins of Various Species, *J. Immunol* **18** 17, 1930.

9 Fuchs, H. J., and von Falkenhausen, M. Remarks on the Work of K. Yokota Concerning the Occurrence of Proteolytic Ferments in Serum *Biochem Ztschr* **237** 87, 1931.

10 Bernhard, F., and Kohler, K. The Diagnosis of Cancer by the Determination of Lipase in Serums and the Ca Reaction of Fuchs, *Deutsche Ztschr f. Chir* **248** 72, 1936.

11 Jedlička, V. and Weichherz, E. The Value of the Fuchs Test *Ztschr f. Krebsforsch* **41** 148, 1934.

confirmed the atypical results with esophageal tumors. Of 126 cases of malignant tumor their results were incorrect in only 6. Kafka<sup>12</sup> obtained 90 per cent accuracy in one series and in another series of 142 cases was 94 per cent correct, using an improved technic.<sup>13</sup> Brandt's<sup>14</sup> findings were correct in 92.5 per cent of 112 cases, those of Latthammer and Rosenbohm,<sup>15</sup> in 72 of 77 cases. Latthammer and Pistofidis<sup>16</sup> compared the Fuchs and the Kahn<sup>17</sup> test for malignant tumor. In 28 proved cases the Fuchs test had an accuracy of 97 per cent as compared with 84 per cent for the Kahn test. In 35 cases of nonmalignant disease the Fuchs test was 97 per cent correct and the Kahn test 86 per cent. Woodhouse<sup>18</sup> described results in 107 cases. He was correct in 50 of 53 cases of malignant tumor and 38 of 42 of nonmalignant disease. Yasumasu<sup>19</sup> diagnosed early stages of carcinoma in 140 cases by the method.

The immunologic aspects of the test have been studied by Fuchs and his co-workers.<sup>20</sup> A rather comprehensive review of the subject<sup>21a</sup> to October 1935 and an article explaining the significance of the reaction were published by Fuchs.<sup>21b</sup>

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12 Kafka, V, Jr. Contributions to the Study of the Fuchs Test, *Ztschr f Krebsforsch* **41** 369, 1934

13 Kafka, V, Jr. Further Experiences with the Fuchs Test, *Ztschr f Krebsforsch* **42** 241, 1935

14 Brandt, E. Experiences with the Fuchs Reaction, *Ztschr f Krebsforsch* **43** 370, 1936

15 Latthammer, R, and Rosenbohm, A. The Fuchs Cancer Reaction, *Ztschr f Krebsforsch* **45** 28, 1936

16 Latthammer, R, and Pistofidis, H. Comparison of the Diagnostic Value of the Cancer Reaction of Fuchs and Kahn, *Ztschr f Krebsforsch* **45** 105, 1936

17 Kahn, H. (a) A Simple Flocculation Reaction of Malignant Tumor, *Klin Wchnschr* **2** 1364, 1923, (b) The Differential Diagnosis of Malignant Tumors with a Few Drops of Blood, *ibid* **3** 920, 1924

18 Woodhouse, D L. Fuchs Serum Proteolysis Test for Malignancy, *Lancet* **1** 138, 1937

19 Yasumasu, T. Serochemical Carcinoma Reaction of Fuchs, *Fukuoka Acta med* **29** 157, 1936, *Jap J M Sc*, IX, Surg, Orthop & Odont **5** 259, 1938

20 Aurin, H, Fuchs, H J, and Kowarzyk, H. Investigations on the Serological Relation Between Embryonic Blood and Blood of Cancer Patients, *Ztschr f Immunitätsforsch u exper Therap* **80** 420, 1933. Fuchs and von Falkenhausen.<sup>4</sup> Fuchs, H J, and von Falkenhausen, M. Tumor-Immunity II The Separation of Tumor-Specific Antigen from Tumor Specific Antibody in Blood Serum, *Ztschr f Immunitätsforsch u exper Therap* **80** 390, 1933. Fuchs, H J, and Kowarzyk, H. Tumor-Immunity I The Formation of Tumor-Specific Antibodies in Living Organisms After Injection of Tumorantigen Containing Serum, *ibid* **80** 375, 1933, Tumor Specificity and Tumor Genesis, *Klin Wchnschr* **15** 289 and 330, 1936

21 Fuchs, H J. (a) The CaR (Cancer Reaction) of Fuchs, *Ztschr f d ges exper Med* **98** 70, 1936, (b) The Significance of the CaR for the Cancer Problem, *Ztschr f Krebsforsch* **44** 384, 1936



Modifications in the method have been suggested by Fuchs and his associates,<sup>22</sup> by Mimbeck<sup>23</sup> and by Caspary,<sup>24</sup> as well as by Wright and Wolf<sup>5</sup>

We have used the test in about 200 cases in the Vanderbilt University Hospital

#### METHOD

The original method of Fuchs called for a substrate of washed fibrin, which was prepared as follows<sup>22c</sup> Blood was drawn into a clean, dry syringe moistened with liquid petrolatum and was at once transferred to a tube. The fibrin was whipped out with a stick, on which it collected. It was kneaded in cold water until all pigment was washed out. The nearly white fibrin was then placed in a bag of cloth with a mesh sufficiently large to permit free access of water but small enough to retain the particles of fibrin. It was suspended in a wide-mouthed vessel in a stream of water rapid enough to keep the fibrin in constant agitation. This washing was continued for eighteen hours. The pure white product was removed from the water, washed repeatedly in distilled water and finally pressed as dry as possible with filter paper. It was then placed on the cloth, which was pinned to a board. A current of air warmed to 30 C was directed against it, which dried it in thirty minutes. It was stored in a vacuum desiccator and remained active for at least nine months. Portions were pulverized in an agate mortar for use as required. This procedure may be modified by drying the fibrin in a vacuum desiccator instead of in a current of air and pulverizing it all for storage.

Another type of substrate was later developed, which had the advantage of furnishing larger quantities of active material from the same amount of blood. It is prepared as follows<sup>22a</sup> The blood is allowed to clot spontaneously, and the serum is centrifuged off. Within ten hours after drawing, the serum is mixed with 11 volumes of 25 per cent trichloroacetic acid which has been warmed to 20 C. The precipitate is thrown down but not packed, and the supernatant fluid is poured off. Fresh trichloroacetic acid solution at a temperature of less than 15 C is added, and the precipitate is stirred into it. The centrifugation is repeated and the fluid is decanted five times. The last time, the precipitate is packed. After the supernatant fluid is poured off, the vessel and the surface of the precipitate are rinsed with distilled water to remove the residual wash fluid, but the precipitate is not disturbed. Water is carefully poured into the vessel without disturbing the precipitate, and the centrifugation is repeated at high speed to squeeze out the residual acid. This is performed three times, the excess fluid being allowed to drain off thoroughly after the last time.

22 (a) Fuchs, H. J. A New Substrate for the Examination of Blood for Malignant Tumors, *Klin Wchnschr* **11** 1997, 1932. (b) Fuchs, H. J., and von Falkenhausen, M. A New Micro Method for the Determination of Nitrogen and Its Application to the CaR. *Biochem Ztschr* **245** 304, 1932. (c) Further Contributions to the Serum Chemical Diagnosis of Malignant Tumors (CaR), *Ztschr f d ges exper Med* **81** 169 1932.

23 Mimbeck, H. New Technic for the Fuchs Reaction for the Diagnosis of Cancer, *Ztschr f d ges exper Med* **96** 362 1935.

24 Caspary, H. An Improved Method for the Fuchs Cancer Reaction, *Ztschr f Immunitatsforsch u exper Therap* **82** 506 1934.

The solid product is finally transferred, as completely as possible to a glass plate, and the plate, centrifuge vessel and spatula are placed in an oven at not over 40 C for three hours. The material from all the utensils is then scraped onto a clean piece of paper and left in the oven overnight. It is finally ground in an agate mortar and stored in the ice box.

Fuchs emphasized the importance of testing each new preparation (1) against normal serum to prove its inactivity against such serum and (2) against foreign serum to determine its activity against this. These tests should never be omitted and, according to our experience, should be repeated at frequent intervals<sup>25</sup>

The test is carried out as follows. Enough blood to give 5 cc of clear serum is drawn in a clean, dry syringe lubricated with liquid petrolatum to prevent hemolysis. It is allowed to clot spontaneously and is then centrifuged. The serum is transferred to a clean, dry test tube.

The next step, the incubation of serum with substrate, may advantageously be carried out in a test tube of more than 12 cc capacity and strong enough to withstand centrifugation. The usual type of pointed centrifuge tube should not be used, because the solid substrate collects in a mass in the tip, exposing a minimal surface to the serum. A test tube may be used, but the supernatant fluid from the subsequent trichloroacetic acid precipitation may have to be filtered. We have used ordinary 150 mm pyrex test tubes with a constriction made at the level of the surface of the trichloroacetic acid precipitate.

For each test four tubes are required. Into each of two of them approximately 5 mg of powdered substrate is measured with a small glass scoop. One cubic centimeter of serum is accurately measured with an Ostwald pipet into each of the four tubes and is thoroughly mixed with substrate. The tubes are then set in a beaker or other convenient vessel, covered with a watch glass or a Petri dish and placed in an incubator at 38 C overnight. Fuchs placed chloroform in the oven to reduce the bacterial growth.

The next day 11 cc of 5 per cent trichloroacetic acid is accurately measured from a buret into each tube and after thorough mixing is allowed to stand for fifteen minutes. The tubes are then centrifuged, and the supernatant fluid is decanted into clean, dry test tubes. Samples of 4 cc each are pipetted into digestion tubes for the estimation of nitrogen by a micro-Kjeldahl procedure. Increases of over 2 mg per hundred cubic centimeters in the substrate tubes indicate a positive reaction.

Although in the work reported here we used all the precautions specified by Fuchs, we since have used chemically clean, but not sterile, technic, have omitted chloroform from the incubator and have never encountered difficulty from microbial contamination. The quantities used are those recommended by Fuchs but may be varied to suit conditions, e g, 14 cc of trichloroacetic acid may be added to the serum and 5 cc aliquots taken for analysis. Filtration may, of course, be substituted for centrifugation of the trichloroacetic acid precipitate. We have found that an incubation period of twelve to eighteen hours gives the best results. Shorter periods give smaller differences, due to incomplete action of the enzyme, other reactions assume significance with longer ones.

The accuracy and delicacy of the nitrogen determination are the crux of the whole procedure. Several methods have been advocated. We have used the manometric one of Van Slyke, though others are doubtless as good.<sup>26</sup>

25 Fuchs and von Falkenhauseu<sup>9</sup> Van der Scheer<sup>8</sup> Yokota<sup>7</sup>

26 Kafka<sup>12</sup> Kahn<sup>17b</sup> Minibek<sup>23</sup>

## RESULTS

We obtained negative reactions in the cases of 74 patients in whom no evidence of a malignant process was found. These included 4 patients with syphilis and 4 with tuberculosis. There were 3 samples of placental blood and 10 samples of blood from patients in the fourth to the seventh month of pregnancy<sup>10</sup>. In 10 cases malignant tumor was suspected but the growth was shown on biopsy to be benign. There were a number of negative values corresponding to Fuchs's "immune reaction," most of which were too small to be significant. Of those which were greater than experimental error, 2 were given by blood from tuberculous patients, 1 by blood from a syphilitic patient and 3 by placental blood or blood from pregnant women.

In 56 cases of proved malignant tumor the Fuchs reaction was positive. This series included 11 cases of carcinoma of the cervix, 9 cases of cancer of the bladder and 3 each of malignant tumor of the face, stomach, breast and jaw. Other growths represented were tumors of the brain, cancer of the ovary, hand, tongue, prostate and pancreas.

The chief interest in these results lies in the wide variety of tumors that give positive reactions. Previous reports in the literature indicate that only esophageal lesions fail to give positive reactions. Why this particular site differs from all others is not known, and further experiment might show this statement to be inaccurate.<sup>7</sup> One case of syphilis is included, but the positive reaction was probably due to the accompanying malignant growth. In 2 cases the growths were recurrent after one to four years.

From the standpoint of evaluating the method the figures in the accompanying table are perhaps the most important, since they indicate the conditions under which it fails. The blood in all cases tabulated gave negative reactions by the Fuchs method, though the patients either had or had previously had proved malignant tumors. By far the greatest number of patients represented in this table had undergone some sort of therapy, after which the tumor showed no signs of recurrence. In other words, as far as could be judged clinically they were cured.

If the assumption is made that the Fuchs reaction would have been positive prior to treatment, it would seem that the effects of therapy are rather prompt, as has been suggested by other investigators.<sup>28</sup> In case 5 a negative reaction was obtained six days after operation. In case 195 the reaction was negative a week after operation. In several negative reactions were obtained after two or three months. Case 147 is particularly interesting in this connection. The patient was given radium on May 26, 1937. On July 28 her blood gave a positive Fuchs reaction. She was operated on three days later. High voltage roentgen therapy

27 Bernhard and Kohler<sup>10</sup> Jedlička and Weichherz<sup>11</sup>

28 Cadness and Wolf<sup>6</sup> Wright and Wolf<sup>5</sup>

*Negative Fuchs Reactions in the Presence of Malignant Tumor or a Past History of Malignant Tumor*

No	Clinical Diagnosis	Comment	Residual Nitrogen Mg /100 Cc of Blood		
			Serum Alone	Serum and Substrate	Differ ence
A Disagreement Explainable					
5	Sarcoma of jaw	6 days after operation	30.89	31.09	0.20
5	Sarcoma of jaw (same case*)	3 weeks after operation	23.13	23.72	0.59
24	Carcinoma of larynx	Roentgen therapy 2 months previously	20.52	20.76	0.24
27	Carcinoma of lip and neck	Roentgen therapy 19 months and operation 14 months before, no recurrence	31.10	31.24	0.14
29	Carcinoma of lip	Operation 1 month before, roentgen therapy in progress	24.42	25.56	1.14
37	Squamous cell carcinoma of cervix	Operation and roentgen therapy 5 weeks before	17.32	17.57	0.25
39	Carcinoma of ear	Roentgen therapy 2 months before no recurrence	31.14	31.00	-0.14
40	Carcinoma of cervix	Operation and roentgen therapy 2 months before	26.26	26.36	0.10
43	Epithelioma of face	Only 5 weeks' duration	31.27	31.59	0.32
49	Carcinoma of mouth	Operation 6 months before	29.38	29.09	-0.29
57	Carcinoma of face	Only 4 weeks' duration	28.93	29.00	0.07
64	Carcinoma metastatic from breast	Operation 2 years and roentgen therapy 3 months previously	24.67	24.57	-0.10
70	Carcinoma of lip	Operation 16 months before recurrence 4 months after this test	35.01	34.71	-0.30
71	Carcinoma of lip	Operation and roentgen therapy 7 months ago	40.86	40.14	-0.72
79	Carcinoma of cervix	Radium and operation 2 months ago	23.01	22.75	-0.26
82	Carcinoma of lip	Only 3 months' duration	34.84	35.20	0.36
83	Carcinoma of cervix	Roentgen therapy in progress	26.20	26.03	-0.17
123	Carcinoma of bladder	Roentgen therapy	36.37	35.98	-0.39
136	Carcinoma of breast	Extensive carcinomatosis of long standing but in remission	26.11	26.22	0.11
137	Melanoma of vulva	2 years old but only 4 months of rapid growth	24.35	24.54	0.19
140	Carcinoma of face	Roentgen therapy	31.89	32.67	0.78
147	Squamous cell carcinoma of cervix	2 weeks after operation (positive before operation)	27.44	27.22	-0.22
159	Adenocarcinoma of uterus	Radium and roentgen therapy 8 years ago	23.99	25.09	1.10
168	Squamous cell carcinoma of cornea	Only 4 months' duration	34.31	35.60	1.39
175	Carcinoma of esophagus		21.27	21.08	-0.19
180	Carcinoma of penis	Three weeks after operation	36.83	36.57	-0.26
191	Carcinoma	12 days after exploratory laparotomy	36.81	37.24	0.43
195	Adenocarcinoma	1 week after operation	49.51	49.45	-0.06
Total, 27 cases					
B Disagreement Not Explainable					
23	Basal cell carcinoma of arm and squamous cell carcinoma of ear		24.51	24.69	0.18
32	Lymphatic leukemia		27.64	28.00	0.36
47	Carcinoma of lungs		35.91	35.49	-0.42
128	Monoblastic leukemia		26.98	26.49	-0.49

*Negative Fuchs Reactions in the Presence of Malignant Tumor or a Past History of Malignant Tumor—Continued*

No	Clinical Diagnosis	Comment	Residual Nitrogen Mg /100 Cc of Blood		
			Serum Alone	Serum and Substrate	Differ- ence
133	Carcinoma of prostate		24.78	25.73	0.96
145	Carcinoma of prostate		50.44	51.84	1.40
152	Adenocarcinoma of cecum		51.61	51.92	0.31
167	Carcinoma of face		24.59	24.90	0.31
171	Adenocarcinoma		33.89	34.53	0.64
174	Carcinoma of testes		30.03	31.74	1.71
182	Carcinoma of rectum		19.42	20.76	1.34
183	Carcinoma of ovary	Recurrence 4 years after operation	25.71	25.97	0.26
183	Carcinoma of ovary (same case*)	24 hours after roentgen therapy	24.53	25.90	1.37
185	Benign hypertrophy of prostate	Malignant at autopsy	99.41	99.57	0.16
187	Carcinoma of cervix		30.33	30.65	0.32
188	Carcinoma		41.52	42.01	0.49
190	Squamous cell carcinoma of cervix		21.33	21.29	-0.04
192	Secondary carcinoma of pelvic bones	Recurrence 9 months after operation	44.45	45.38	0.93
198	Wilms' embryoma		24.93	25.35	0.42
Total 18 cases					

\* Cases in which a negative reaction was twice obtained are included only once in computing the total number of cases

was then given and was repeated beginning December 13. On Feb 15, 1938 her blood still gave a positive reaction. On March 1 it gave the negative reaction reported in the table. At this time and one week later she was much improved. She did not return to the hospital. She died June 15 in another city, of "locked bowels." That the test measures the activity of the malignant growth is indicated by case 136. On admission the patient was found to have extensive carcinomatosis with metastases to the bones and other structures. At this time her blood gave a positive Fuchs reaction. She was pregnant and was delivered by cesarean section, receiving several transfusions but no treatment for the malignant tumor. Two months later she returned to the hospital. Blood was taken and gave the negative reaction recorded in the table. At this time she was much improved, she had gained weight, and there was marked retrogression of her osseous lesions. Several months later, however, she died.

A third case indicating that operative procedure alone may affect the result was observed (case 191). The blood gave a positive Fuchs reaction on July 29, 1938. An exploratory laparotomy was performed when a biopsy specimen was taken, but nothing more was done. On August 10 a second sample of blood was taken, which gave the negative result reported in the table.

In case 175 the growth was a carcinoma of the esophagus, which, as has been stated, is said to be associated with a negative reaction of the blood

In 4 of the cases reported the growths were respectively of four weeks', five weeks', three months' and four months' duration, the onset being pretty accurately determinable because of the superficial character of the growth. In a fifth, although the growth was about two years old, it had shown rapid growth only during the four months preceding the examination. The false negative reactions may, therefore, be explained by the assumption that the production of enzymes does not reach a detectable level for over five months. A similar case (not included in this group because no microscopic examination was made, though the diagnosis is probably correct) adds weight to this assumption. There are 27 examples in the table (section *A*) of patients who were cured, were under treatment or had lesions in the early stages of growth.

There remain in this group (section *B* of table) 18 cases in which no explanation appears and in which the results of the Fuchs test must be assumed to be genuine false negative reactions.

In 5 other cases the Fuchs reaction was positive in spite of the fact that the pathologists failed to find malignant tissue. This, of course, does not mean that such tissue was not present in some other part of the body.<sup>10</sup>

We also have data on 13 cases in which no microscopic examination was made.

Other investigators have reported that false negative reactions are seldom obtained but that false positive reactions may be obtained in a number of conditions, notably syphilis and tuberculosis. Our experience has not confirmed this. We have had no positive results from either of these diseases and have obtained more false negatives than false positive reactions. From experiences subsequent to the completion of this work, we feel that the accuracy of the method could be materially increased by improving the quality of the substrate and by frequent checking of its activity. The fact that this was not done may account for a number of our failures. After completion of this work no tests with old substrate were made for several weeks when a negative result was obtained in a proved case of malignant tumor. Investigation revealed that all samples of substrate had become inactive. Since that time we have been unable to prepare an active trichloroacetic acid substrate, though active fibrin ones have been prepared consistently. The explanation for this failure has not yet been found. We suspected poisoning of the enzyme by traces of heavy metals in the reagents, but using water redistilled from glass to make up all solutions and to recrystallize the trichloroacetic acid did not change the results.

The mechanism of the reaction is still obscure and should be studied. Apparently, the substrate participates in the reaction in an active way. If it does serve merely as a protein on which serum protease acts, it must be an unstable one which can change on standing.

#### SUMMARY

The Fuchs test for malignancy is a chemical laboratory procedure which can be performed with 15 cc of blood. Although there is a strong correlation between the results of this test and the pathologic observations, it apparently has certain limitations: (1) The growth must be over six months old, (2) the patient should not have been operated on or have received radium or roentgen treatment for at least a month, and (3) the tumor must be in a period of active growth.

Dr. Henry Douglas, Dr. J. C. Pennington and other members of the staff of Vanderbilt University Hospital supplied the clinical material for this work.

# BACILLUS PYOCYANEUS OSTEOMYELITIS OF THE SPINE

REPORT OF A CASE OF SUCCESSFUL TREATMENT  
WITH SULFANILAMIDE

ALBERT J SCHEIN, M D

Adjunct Orthopedist, Mount Sinai Hospital, Assistant Visiting  
Orthopedic Surgeon, Bellevue Hospital

NEW YORK

The case to be presented is unique for several reasons. It is the first case of osteomyelitis due to *Bacillus pyocyaneus* to be reported in the literature. It is the only case of spinal skeletal involvement by this organism which could be found. Finally, it is one of the few cases in which sulfanilamide therapy was tried and appeared effective.

The literature on infections due to *B. pyocyaneus* (*Pseudomonas aeruginosa*) has been reviewed in detail in several papers in the past twenty-five years.<sup>1</sup> No effort will be made to repeat this work. The organism is not uncommonly encountered in infected wounds of various types, especially large granulating areas. Ordinarily it is only slightly pathogenic, is easily controlled by applications of boric acid and presents no problem. It is recognizable by its color and odor. Occasionally, however, it becomes a dangerous pathogen, invading visceral cavities, mucous membranes and even the blood stream, with secondary localizations.

Infections of the genitourinary tract are especially likely to be due to this bacillus. In a recent discussion of a case of *B. pyocyaneus* meningitis, Slutsky and Matlin<sup>2</sup> reviewed the incidence of invasion of the blood stream following manipulations of the genitourinary tract. They reported that when routine cultures of the blood were made in

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From the Orthopedic Service of Drs. R. K. Lippman and S. Selig and the Medical Service of Dr. B. S. Oppenheimer, the Mount Sinai Hospital.

1 (a) Epstein, J. W., and Grossman, A. B. *Bacillus Pyocyaneus* Infections in Children, *Am J Dis Child* **46** 132 (July) 1933. (b) Brown, C. F. C. *Bacillus Pyocyaneus* Infections, *M Clin North America* **14** 1243 (March) 1931. (c) Fraenkel, E. Weitere Untersuchungen über die Menschenpathogenität des *Bacillus pyocyaneus*, *Ztschr f Hyg u Infektionskr* **84** 369, 1917.

2 Slutsky, N., and Matlin, P. *Pyocyaneus* Meningitis, *J A M A* **113** 1400 (Oct 7) 1939.



investigation of chills after such instrumentation, Scott<sup>3a</sup> found 3 of 82 "positive" cultures yielding *B. pyocyaneus*, while Hyman and Edelman<sup>3b</sup> reported 1 of 63 "positive" cultures as yielding this organism. In addition, individual cases of infection with a similar portal of entry have been reported by others<sup>3c</sup>. In adults this is probably the most common source of entry of the organism, others being by way of the gastrointestinal tract and by way of discharging surgical wounds. In children general infection usually arises from involvement of the skin in the form of ecthyma, as reported by Epstein and Grossman.<sup>1</sup>

Lesions of the skeletal system caused by this organism have rarely been reported, as compared with frequent reports of pyelitis, ecthyma and meningitis. Epstein and Grossman mentioned 2 cases of suppurative arthritis. One was a case of sepsis of the hip, published by Groves<sup>4</sup> in 1909, the condition was successfully treated by incision and drainage with use of autogenous vaccine. The other was a case of a suppurating knee which required amputation, reported by Wassermann<sup>5</sup> in 1901. In 1927, Pinelli<sup>6</sup> described a case of suppuration of the left shoulder, in this case also the condition was cured by incision and drainage combined with use of autogenous vaccine. Finally, Bishop<sup>7</sup> recently reported a case of suppurative arthritis of the ankle due to direct invasion by *B. pyocyaneus* from pyoderma in an extensive burn. In this case, again, the condition was cured by incision and drainage of the ankle and use of autogenous vaccine. No case of hematogenous osteomyelitis due to this organism has been discovered.

Until recently there has been no acceptable specific therapy for systemic infection by *B. pyocyaneus*. Autogenous vaccines have been used for many years, almost since discovery of the pathogenic properties of the germ. Fraenkel,<sup>1c</sup> in 1917, in an exhaustive review of 26 cases, stated that autogenous vaccines are of little use, since 83 per cent of the

3 (a) Scott, W. W. Blood Stream Infections in Urology. Report of Eighty-Two Cases. *J. Urol.* **21** 527 (May) 1929. (b) Hyman, A., and Edelman, L. Medical and Surgical Aspects of Hematogenous Infections in Urology, *ibid.* **28** 173 (Aug.) 1932. (c) Barrington, F. J. F. and Wright, H. D. Bacteremia Following Operations on Urethra, *J. Path. & Bact.* **33** 871 (Oct.) 1930. Powers, J. H. Renal Function Following Trauma of Kidney. Clinical and Experimental Study, *New York State J. Med.* **36** 1411 (Oct. 1) 1936. Ewell, G. H. *Bacillus Pyocyaneus* Bacteremia Secondary to Pyelonephritis and Prostatic Abscess with Death. Case Report, *Urol. & Cutan. Rev.* **40** 697 (Oct.) 1936.

4 Groves, E. H. A Clinical Lecture on a Case of *Bacillus Pyocyaneus* Pyaemia Successfully Treated by Vaccine, *Brit. M. J.* **1** 1169 1909.

5 Wassermann, A. Septische Nabel-Infektion Neugeborener. Ein Beweis für die *B. Pyocyaneus* beim Menschen. *Virchows Arch. f. path. Anat.* **165** 342 1901.

6 Pinelli, A. Artrite monoarticolare primitiva da piociano. *Pediatria* **35** 147 (Feb. 1) 1927.

7 Bishop, W. A., Jr. A Case of Primary *Bacillus-Pyocyaneus* Arthritis in an Infant, *J. Bone & Joint Surg.* **20** 216 (Jan.) 1938.

infections end fatally, despite publication of occasional individual successes in treatment Soeters,<sup>8</sup> in 1937, first reported a case of sepsis due to this organism treated with a derivative of sulfanilamide ("prontosil soluble," now known as azosulfamide, disodium sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6' disulfonate) and repeated blood transfusions, recovery occurred Stewart and Bates<sup>9</sup> thereafter pointed out that others of the same family of organisms, such as *Bacillus typhosus* and *Bacillus coli*, are susceptible to the action of sulfanilamide in animals and probably in human beings They reported a case of infection of the gastrointestinal and urinary tracts successfully treated by the drug Helmholz<sup>10</sup> and Long and Bliss<sup>11</sup> have mentioned the efficacy of sulfanilamide in clearing the urine of *B. pyocyaneus* The latter authors have estimated that a urinary concentration of sulfanilamide of 300 mg per hundred cubic centimeters is required to sterilize the urine of this organism

#### REPORT OF CASE

A 56 year old Irishman, single, was admitted to the medical service of Dr B S Oppenheimer at the Mount Sinai Hospital on May 28, 1938 and discharged October 4

In his youth he had had infectious disease of the right hip with a discharging sinus for over two years This had become and remained quiescent, with fibrous ankylosis of the joint On two occasions, ten and five weeks respectively before admission, the patient had attacks of colicky pain in the right loin, radiating to the right pubic region, relieved by hypodermic medication after several hours and unaccompanied with hematuria, chills or fever Because of this he was examined for renal calculi, and the cystoscope was used eight days before admission On the next day he vomited and had severe pain in the loin and high fever Prostration was marked for a week On the day before admission he had a severe shaking chill, a temperature of 106 F and delirium There was a little pain in the right loin at the time of admission

*Physical Examination*—The patient was well developed and acutely ill The heart and lungs were normal, the abdomen was soft Bilateral tenderness in the costovertebral angles was present, more marked on the right The prostate gland was moderately and diffusely enlarged The left hip was stiff, with much atrophy of the surrounding muscles but no localized tenderness or pain There were two small healed scars on its outer aspect

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8 Soeters, J M Pyocyaneus Sepsis in a Child Recovery with Prontosil, *Maandschr v kindergeneesk* 7 74 (Nov) 1937

9 Stewart, W, and Bates, T *Bacillus Pyocyaneus Infections A Case Treated with Sulfanilamide*, *Lancet* 1 820 (April 8) 1939

10 Helmholz, H F Bactericidal Power of Urine After Administration of Prontylin by Mouth, *Proc Staff Meet, Mayo Clin* 12 244 (April 21) 1937

11 Long, P H, and Bliss, E A The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939

*Early Laboratory Data*—The value for hemoglobin was 71 per cent. The red blood cells numbered 4,800,000 per cubic millimeter. The white blood cells numbered 10,100 per cubic millimeter, with 90 per cent polymorphonuclear leukocytes, showing marked toxic granulation.

The urine was alkaline, the specific gravity was 1.015. There was a trace of albumin. Microscopic examination showed red and white blood cells, and there was a pure culture of *B. pyocyaneus*.

The Wassermann reaction of the blood was negative, and the value for blood urea was 31 mg per hundred cubic centimeters. A culture of blood taken on admission was sterile after four days.

Roentgen examination of the abdomen (genitourinary flat plate) showed a left renal calculus and a second small concretion on the right side, near the pelvic

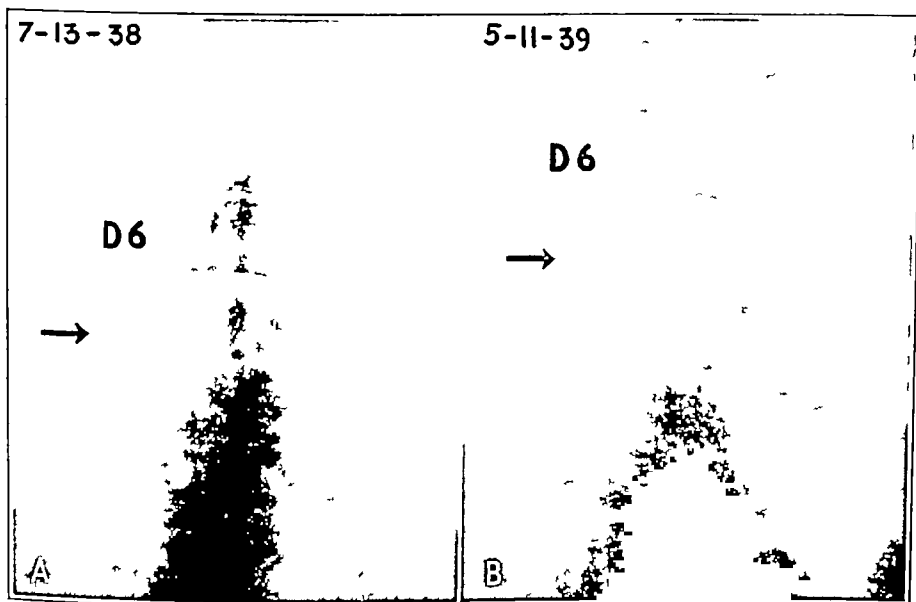


Fig 1—Lateral view of the dorsal portion of the spine, showing the course of infection (A and B) and the final fusion (C)

rim, in the course of the ureter. The left hip gave evidence of old quiescent destructive osteoarthritis. The thoracic film showed a bilaterally elevated diaphragm, with a linear shadow of atelectasis above the left leaf.

Examination and culture of material from the stool gave negative results.

*Diagnosis*—The patient was assumed to have pyelonephritis and possibly prostatitis (following use of the cystoscope) with left renal and right ureteral calculi. The chills and fever were considered to be due to invasion of the blood stream by some organism, to be identified.

*Course of Infection*—Administration of large quantities of fluids, a purgative dose of castor oil and citrates was begun at once. Four grams of sulfanilamide was given daily. This dose was later reduced, and administration of the drug was stopped after nine days, when a total of 27 Gm had been given. The temperature,

which rose to 106 F shortly after admission, "spiked" from 99 to 106 F for two days and then dropped to practically normal. The patient became anorectic, depressed and slightly disoriented, which was the cause for discontinuing the medication.

One and one-half weeks after admission, pain in the back was present when the patient raised himself in bed, and exquisite tenderness was elicited over the lower dorsal segments of the spine. Tenderness of the costovertebral angles was minimal. The temperature, which had been normal for some time after discontinuance of sulfanilamide therapy, began to rise irregularly to from 102 to 103 F daily, and the patient again appeared acutely ill. Although it was the general suspicion that a metastatic focus had lodged in a dorsal vertebra, it was some weeks before roentgen confirmation was obtained. Two separate roentgen examina-

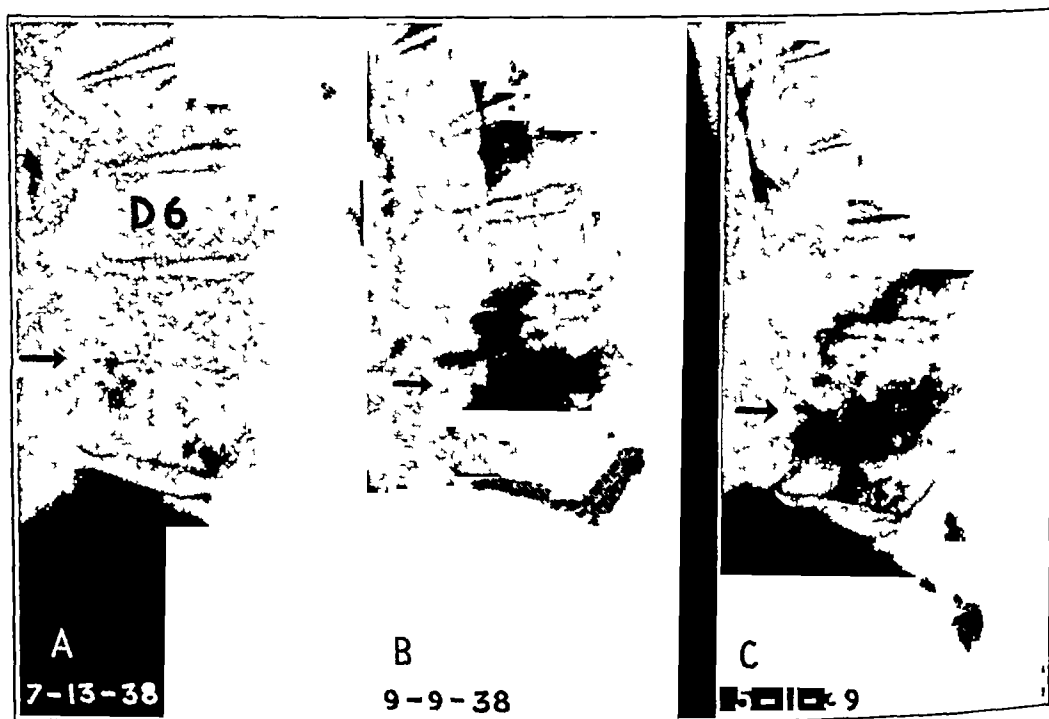


Fig 2—Anteroposterior views of the dorsal portion of the spine. *A* shows the lesion between the seventh and the eighth dorsal vertebra, *B*, the final fusion.

tions, on June 6 and 24, showed no changes in the dorsolumbar portion of the spine other than mild hypertrophic arthritis.

Repeated cultures of the urine, on June 1, 4, 6, 11, 20 and 27 and July 31, as well as later (on August 25), all yielded *B. pyocyaneus*. A second culture of blood, taken in June 27, during a rise in temperature above 102 F, showed a pure growth of *B. pyocyaneus* in one flask. The sedimentation rate was 18 mm in twenty minutes, indicating the activity of the general infection. Chemical study of the blood on June 22 showed a carbon dioxide-combining power of 54.9. The value for calcium was 9.8 mg, that for phosphorus 3.6 mg, that for urea 32 mg and that for sugar 75 mg per hundred cubic centimeters. On July 7 the value for blood urea was 7 mg per hundred cubic centimeters, and the icteric index was 9. An intravenous pyelogram taken on June 28 showed the left calculus in the ureter and the right one low in the ureter.

Sulfanilamide was administered again when the infection could not be controlled (from July 5 to 10 inclusive), in larger doses than before, a total of 34 Gm being given. The temperature subsided and remained low for the remainder of the patient's stay in the hospital. Acidification with large doses of mandelic and gluconic acids was tried in an attempt to sterilize the urine, but pyuria and pyocyanuria persisted despite a  $p_{H}$  of 5.2. Two transfusions of citrated blood, 500 cc each, were given to combat the anemia after the value for hemoglobin fell as low as 52 per cent.

As local tenderness over the lower dorsal segments of the spine grew more definite, root zones of cutaneous hyperesthesia appeared. On July 13, seven weeks after the first clinical evidence of sepsis, new roentgenograms of the dorsal portion of the spine showed narrowing of the seventh dorsal interspace, with definite erosion of the adjacent cortical plates of the seventh and eighth dorsal vertebral bodies. There was suggestive widening of the mediastinal structures at this level, probably due to a soft tissue abscess or to infiltration. It was now evident that the patient had acute osteomyelitis of the dorsal portion of the spine, secondary to urosepsis. A gibbus was noted at the eighth dorsal vertebra, and consultation with an orthopedist resulted in the decision that an operation was unwarranted in view of amelioration of the symptoms by sulfanilamide.

A plaster jacket was applied on July 20, and the pain immediately subsided. The remainder of the stay in the hospital was uneventful, the patient being kept recumbent almost to the time of discharge, when he was transferred to the Montefiore Hospital for Chronic Diseases for convalescent care. The value for hemoglobin was 70 per cent on his discharge, and a congo red test showed no evidence of amyloidosis. Further roentgen studies of the dorsal portion of the spine on September 6 and 9 showed an increase in size of the paravertebral mass with further destruction of the opposing vertebral surfaces.

At the Montefiore Hospital, convalescence continued uneventfully. The patient stayed there from October 4 to April 23, 1939. Culture of the urine continued to show *B. pyocyaneus*, and a ureteral calculus was still visible on the left side. The plaster jacket was worn for several months and then was replaced by a high Knight spinal brace. The patient was ambulatory and had very few symptoms at the time of discharge.

On May 11 the patient appeared at the Mount Sinai orthopedic follow-up clinic and was found to be clinically well, with good motion of the spine.

Roentgen examination showed disappearance of the intervertebral space between the seventh and eighth dorsal vertebrae, as well as of the soft tissue shadow. In September, fusion of the involved vertebral bodies was considered solid, and the brace was finally discarded. There was no local tenderness, but slight residual gibbus and occasional local pain were present.

#### COMMENT

The diagnosis of *B. pyocyaneus* urosepsis following cystoscopic procedures for renal calculus, complicated by *B. pyocyaneus* osteomyelitis of the dorsal portion of the spine would seem to be established by the septic picture, the repeated pure cultures of the organism from the urine and, above all, the blood culture yielding the same organism which can hardly have been a contaminant. Nevertheless, at the time of transfer, the possibility of Pott's disease following childhood tuberculosis of the hip was considered, the urinary sepsis then being inter-

preted as incidental. Against this are the rapid response of the febrile infectious picture to administration of sulfanilamide and the course of the spinal infection. Healing of the lesion of the dorsal portion of the spine in a year and a half by fusion of the involved vertebrae with good calcification is unlike Pott's disease but is compatible with infectious osteomyelitis due to a pyogenic organism.

#### SUMMARY

It is shown that the ordinarily saprophytic *B. pyocyaneus* may under certain circumstances become pathogenic and invasive and may cause septicemia with secondary localization.

In adults, one of the most common portals of entry is by infection of the urinary tract, especially after operation or other instrumentation.

A case is reported in which this occurred with secondary localization in the dorsal portion of the spine. This is the first case of *B. pyocyaneus* osteomyelitis to be reported in the literature.

It took seven weeks, during which there were negative results on two examinations, to demonstrate the suspected spinal lesion roentgenographically.

Sulfanilamide controlled the original sepsis but did not prevent localization in the spine.

Further administration of sulfanilamide controlled the sepsis, which had recurred.

Subsequent treatment by orthopedic measures resulted in healing by fusion of the spine in less than one and one-half years.

# INCOMPLETE INDIRECT INGUINAL HERNIAS

A STUDY OF 2 462 HERNIAS AND 2 337 HERNIA REPAIRS

HAROLD J SHELLEY, MD

FORT WORTH, TEXAS

A study was made of all hernias in patients admitted to the wards of St Luke's Hospital, New York, from 1926 to 1935 inclusive. Also included in the study were all hernias repaired from 1916 to 1925 inclusive which were observed postoperatively for nine months or longer. This gave a total of 4,442 hernias, of which 2,462, or 55.4 per cent, were incomplete indirect inguinal hernias. They made up 67.4 per cent of all inguinal hernias included in the study.

Of these 2,462 hernias, 2,337 were repaired. Among the 1,668 which were followed for nine months or longer (the average follow-up time was thirty-six months), 120 recurrences were found, an incidence of 7.2 per cent. The average time after operation at which these recurrences were first noted was thirty-two and two-tenths months.

## ETIOLOGIC FACTORS

*Age at Onset*—The age at which the hernia was first noted must of necessity be taken as the closest possible approximation of the patient's age at the time of development of the hernia. In this series of cases this figure varied between 1 day and 75 years, the average being 30.9 years.

For the first three five year periods of life the incidences were between 4.3 and 6.5 per cent, increasing to 8.4 per cent between the fifteenth and the twentieth year. The five year groups between the ages of 20 and 40 years showed approximately the same incidences, varying between 10.8 and 12.7 per cent. Following these incidences, the four greatest, the incidences decreased gradually with each five year period to 0.3 per cent for each of the two between the ages of 65 and 75 years.

Grouped into twenty year periods of life, the incidences were: first period, 23.6 per cent, second, 46.9 per cent, third, 27.5 per cent, and fourth, 2.5 per cent.

Recurrence rates increased with increase in the age of the patients at the time the hernias were first noted. For the first twenty years of life the recurrence rate was 2.8 per cent, from the age of 20 to 40 years,

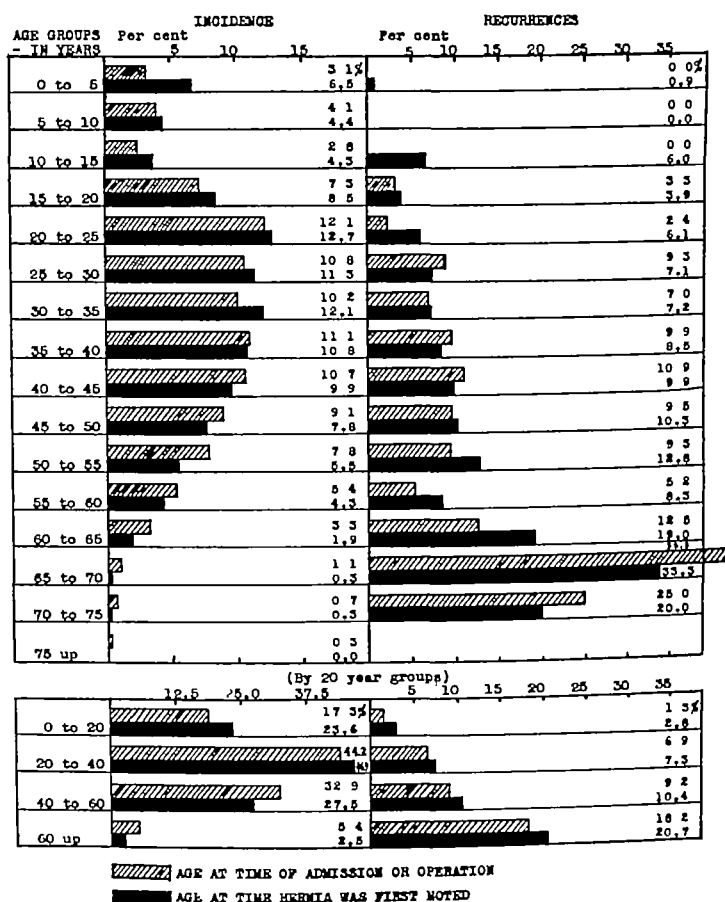
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From the Surgical Services of St. Luke's Hospital

7.3 per cent, from 40 to 60 years, 10.4 per cent, and from 60 to 75 years, 20.7 per cent

*Age at Admission or Operation*—The age of the youngest patient at the time of admission or operation was 1 day, and that of the oldest, 93 years. The average age was 34.8 years.

Only 17.3 per cent were admitted or operated on in the first twenty years of life, and in this group the recurrence rate was 1.3 per cent. Nearly half (44.2 per cent) were admitted or operated on between the



Age incidence

ages of 20 and 40, with a recurrence rate of 6.9 per cent, 32.9 per cent between 40 and 60, with a recurrence rate of 9.2 per cent, and 5.3 per cent between 60 and 80, with 20 per cent of recurrences.

*Sex*—The incidence of males in this group of cases of incomplete indirect inguinal hernia was 88.7 per cent and that of females 11.3 per cent. This is explained by the differences in shape of the male and female pelvises, the presence of the spermatic cord in the male and the much greater incidence of strenuous occupations among males.

The same factors account for the difference in the recurrence rates, which were 7.5 and 4.9 per cent respectively. Difficulty in getting



employed men to leave their work to come in for follow-up examinations was the reason that a somewhat larger percentage of women were examined postoperatively

*Race*—The relative incidence of the three races (table 4) in the group of patients covered by this study is no indication of the relative frequency with which hernias occur among those races. Instead, the figures approximate closely their proportions among the general admissions to the hospital

TABLE 1—*Age at Which Hernia Was First Noted*

Age Group (in years)	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recur rences	Per Cent Recurrences
0 to 5	159	0.5	112	1	0.9
5 to 10	100	4.4	75	0	0.0
10 to 15	106	4.3	83	5	6.0
15 to 20	203	8.4	152	0	3.9
20 to 25	312	12.7	212	13	6.1
25 to 30	288	11.3	108	15	7.1
30 to 35	208	12.1	104	14	7.2
35 to 40	265	10.8	170	15	8.5
40 to 45	244	9.0	162	16	9.9
45 to 50	192	7.8	126	13	10.3
50 to 55	125	5.5	86	11	12.8
55 to 60	97	4.3	60	5	8.3
60 to 65	44	1.9	21	4	19.0
65 to 70	7	0.3	3	1	33.3
70 to 75	8	0.3	5	1	20.0
Totals	2,462	100.0 100.0	1,603	120	7.2 7.2

The average age of the patients when incomplete indirect inguinal hernias were first noted was 30.9 years

That the incidence of recurrences should be less among Negroes than among white patients, 4.9 per cent as compared to 7.5 per cent, is of interest and possibly can be accounted for by the fact that the average Negro patient has better muscular development than has the average white patient. On the other hand the relatively small number of repairs done on Negro patients may not have given a true picture of the incidence of recurrence in this race.

*Trauma*—The accuracy of a history of definite trauma as an etiologic factor in the development of incomplete indirect inguinal hernias must rest to a large degree on conjecture. Unless a patient has been

TABLE 2—*Age at Admission or Operation*

Age Group (in Years)	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recur- rences	Per Cent Recurrences
0 to 5	76	3.1	52	0	0.0
5 to 10	102	4.1	73	0	0.0
10 to 15	70	2.8	49	0	0.0
15 to 20	179	7.3	125	4	3.3
20 to 25	298	12.1	207	5	2.4
25 to 30	266	10.8	172	16	9.3
30 to 35	252	10.2	172	12	7.0
35 to 40	282	11.1	199	19	9.9
40 to 45	263	10.7	174	19	10.9
45 to 50	225	9.1	158	15	9.5
50 to 55	185	7.8	129	12	9.3
55 to 60	131	5.3	94	5	5.2
60 to 65	82	3.3	48	6	12.5
65 to 70	26	1.1	9	5	55.5
70 to 75	17	0.7	8	2	25.0
75 to 80	4	0.2	0		
80 to 85	3	0.1	1	0	0.0
85 to 90	0	0.0			
90 to 95	1	0.04	0		
Totals	2 462	100.0 100.0	1,668	120	7.2 7.2

The average age at the time of admission or operation for incomplete indirect inguinal hernias was 34.8 years

TABLE 3—*Sex*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postop- eratively	Number of Recur- rences	Per Cent Recur- rences
Male	2,184	88.7	1 463	110	7.5
Female	278	11.3	205	10	4.9
Totals	2 462	100.0	1 668	120	7.2

TABLE 4—*Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postop- eratively	Number of Recur- rences	Per Cent Recur- rences
White	2 293	93.4	1 560	114	7.3
Black	161	6.5	107	6	5.6
Yellow	3	0.1	1	0	0.0
Totals	2 462	100.0	1 668	120	7.2

examined immediately before a certain specific trauma considered to be the cause of a hernia, it is impossible to tell in any individual case whether the trauma was the actual cause of the hernia or only the cause of pain in an undiscovered preexisting hernia, with resultant discovery of that hernia. Also, the one definite trauma may have increased the size of the preexisting hernia, so that a previously unnoticeable hernia could be seen.

The figures listed in table 5 are based entirely on the history as given by the patient. It must be taken for granted that no hernia was present before the trauma occurred. Of course, a definite number of these patients had either a known or an undiscovered hernia before the trauma, but there is no possible way to eliminate them from the statistics.

TABLE 5—*History of Definite Trauma As an Etiologic Factor\**

History of Trauma Given as Cause*	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Absent	1 806	73.3	1 217	95	7.7
Positive	656	26.7	451	25	5.5
Totals	2 462	100.0	1 668	120	7.2

\* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied a history of definite trauma as the etiologic factor in the development of their hernias was given by 26 per cent of the patients who first noted their hernias after the age of 15 years (Shelley H. J. Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs. South Surgeon 9: 257-268 [April] 1940).

Slightly over one fourth of the patients, 26.7 per cent, gave a history of a definite trauma as the cause of the development of their hernias. The difference in recurrence rates, 7.7 per cent as contrasted to 5.5 per cent, was almost identical with that occurring between the white and the Negro races, possibly for much the same reason. The patients who gave a history of trauma as the cause of their hernias were on the average more muscular than those who did not give such a history. Also, one would expect to find poorer tissues to work with (again, on the average) among patients in whom a hernia developed without definite trauma than among those in whom a definite trauma was required to cause the hernia. Another factor was that hernias definitely caused by trauma are much oftener operated on sooner than those not falling within this classification, and they were on the average smaller.

#### SYMPTOMS

*Pain*—Pain as a symptom associated with incomplete indirect inguinal hernias was noted in 49.7 per cent of the cases studied and was denied or not mentioned in 50.3 per cent.

Except for pain, as has been noted, the hernias were the cause of symptoms in practically none of the patients unless incarceration or strangulation was present. A visible bulge over the external ring or in the scrotum was noted in 73.3 per cent of the patients.

*Duration*—The duration of the hernias in this group of patients as listed in table 7 was the interval between discovery of the hernia and surgical repair of the hernia or admission of the patient to the hospital.

TABLE 6—*Pain Associated with Hernias*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	1 238	50.3
Positive	1 224	49.7
Totals	2 462	100.0

TABLE 7—*Duration (Time Hernia was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
To 1 week	220	9.0	139	10	7.2
To 1 month	539	21.8	351	25	7.1
First 6 months	1 041	42.3	696	41	5.9
Second 6 months	324	13.1	229	21	9.1
To 1 year	1 365	55.4	925	62	6.7
0 to 10 years	2 136	86.6	1 446	95	6.6
10 to 20 years	217	8.8	146	16	11.0
20 to 30 years	71	2.9	51	5	9.8
30 to 40 years	24	1.0	16	1	6.3
40 to 50 years	11	0.4	7	2	28.6
50 to 60 years	2	0.08	2	1	50.0
60 to 70 years	1	0.04	0	—	—
Totals	2 462	100.0	1,638	120	7.2

The average duration (i.e., the time from which the hernia was first noted to admission or operation) of the 2 462 indirect inguinal hernias was 3.9 years.

This is not the exact figure for actual duration of the hernia in every case, but it is the closest possible approximation. Many of the hernias were undoubtedly present for a considerable period before they were first discovered.

The greatest incidence, considering the period covered, was in the duration of up to one week, 9 per cent. Likewise, the greatest incidence for any duration ending in any one month was found in the first month, 21.8 per cent. The same held true for the first six months, 42.3 per cent, and for the first year, 55.4 per cent. Only 13.1 per cent of the hernias had been noted for periods ranging from six months to one year.

A great majority, 86.6 per cent, had been present for ten years or less. Only 8.8 per cent had a duration of ten to twenty years, and the rates in the succeeding ten year periods were negligible. The average duration was three and nine-tenths years.

*Recurrences*—For the hernias of this type with a duration of up to one month the incidence of recurrences was the same as the average for the entire group studied, 7.2 per cent, up to one week, and 7.1 per cent, up to one month. Hernias with a duration of up to six months showed a lower incidence of recurrences, 5.9 per cent. The rate for the second six month period was one third greater, 9.1 per cent. For the first one year period it was slightly less than the average, being 6.7 per cent.

With the exception of the fourth ten year period, which presented a recurrence rate of only 6.3 per cent, the recurrence rate tended to increase with an increase in the time the hernia had been noted preoperatively. The last four ten year periods listed contain too few followed repairs to yield accurate figures for the respective recurrence rates.

#### PHYSICAL FINDINGS

In a consideration of the physical factors which are of importance in estimation of the probability of the permanence of surgical cure of an incomplete indirect inguinal hernia, a number of these factors, and factors which are of primary importance, cannot be tabulated and used in the calculations. The thickness, strength and position of the various structures making up the internal ring, the walls of the inguinal canal and the external ring fall within this category, as do the various factors determining the individual patient's healing power, the strength of the resultant scar tissue and the strain which may be thrown on the inguinal region subsequent to the repair, particularly by a change of occupation on the patient's part or by unexpected and unusual trauma.

*Size*—In classifying incomplete indirect inguinal hernias as to size, an arbitrary classification must necessarily be chosen. The one described later in this section was considered to be the only one into which these hernias could be definitely classified as to size. It has two major weaknesses as a measure of the condition in relation to the probability of recurrence. In the first place, it does not give an accurate indication of the diameter of the weakened area through which the hernia protrudes, and in the second place, there is a considerable variation in size within each group listed.

These hernias were divided according to size into three groups. Under size I were listed all hernias in which the sac lay entirely within the inguinal canal. Under size II were placed those in which the sac protruded from the external inguinal ring but did not extend into the scrotum. Under size III were classified those in which the sac extended into the scrotum.

The smallest number fell within size I (26·7 per cent), the greatest number, size II (40·7 per cent), and the remainder (32·6 per cent), size III (table 8)

*Recurrences*—Recurrences occurred about equally with sizes I and II (6·2 and 5·7 per cent respectively), with a 50 per cent increase in size III, the figure being 9·8 per cent

*Mortality*—The mortality figures for sizes I and II were 0·27 and 0·18 per cent, and the deaths occurred in patients without either strangulation or incarceration. With size III the mortality was 1·08 per cent, but of the 5 deaths making up this figure 1 occurred in a case of incarcerated hernia and 2 in cases of strangulated hernia. The mortality figure for this group, not including the 2 deaths due to strangulation of the hernias, was 0·65 per cent, which, although small, is still three times the average mortality rate for sizes I and II (0·22 per cent)

TABLE 8—Size

Size of Hernia*	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	657	26·7	437	27	6·2	1 in 366 operations	0·27
Size II	1,003	40·7	682	39	5·7	1 in 544 operations	0·18
Size III	802	32·6	549	54	9·8	5 in 464 operations	1·08
Totals	2,462	100·0	1,668	120	7·2	7 in 1,374 operations	0·51

\* Size I   Hernias in which the sac was limited to the inguinal canal  
Size II   Hernias in which the sac extended beyond the external ring but not into the scrotum  
Size III   Hernias in which the sac extended into the scrotum

(Mortality rates were calculated only from the operations performed in the ten year period from 1926 to 1935)

BILATERAL HERNIAS

The subject of bilateral inguinal hernias is always of interest because of the increased possibility of recurrence when this condition is present and also because of the necessity of making a decision as to the advisability of performing the two repairs at one or at two operations

In a consideration of this subject, those incomplete indirect inguinal hernias which occurred on one side when there was or had been an inguinal hernia of any type on the other side were classified as bilateral hernias. This could be done, as each hernia was considered individually in making up these figures. Also included under bilateral incomplete indirect inguinal hernias were those which occurred in patients who at one time had had a single incomplete indirect inguinal hernia repaired and then, later, an inguinal hernia of any type on the opposite side

*Incidence*—Of the 2,462 incomplete indirect inguinal hernias studied, only 32.7 per cent were bilateral, 67.3 per cent being unilateral. The latter figure is made up of the figures 38.7 per cent for the right side and 28.6 per cent for the left, i. e., 57 per cent of the unilateral hernias were found on the right and 43 per cent on the left. Of the total number of hernias studied in this group, 55 per cent were on the right side and 45 per cent on the left.

*Recurrences*—The recurrence rate for all bilateral incomplete indirect inguinal hernias was 50 per cent greater than for unilateral hernias, the figures being 9.0 and 6.3 per cent respectively. Comparison of the recurrence rates for the two sides showed figures essentially the same for

TABLE 9—Unilateral and Bilateral Hernias \*

	Total Hernias	Per Cent of Entire Group	Number Followed Postop- eratively	Number of Recur- rences	Per Cent Recur- rences
Unilateral right	953	38.7	637	38	6.0
Unilateral left	700	28.6	473	32	6.8
Total unilateral	1,653	67.3	1,110	70	6.3
Total bilateral	803	32.7	558	50	9.0
Total right	1,354	55.0	917	64	7.0
Total left	1,108	45.0	751	56	7.5
Totals	2,462	100.0	1,668	120	7.2

\* All hernias were counted individually. Each incomplete indirect inguinal hernia was considered one of two bilateral hernias when there was or had been an inguinal hernia of any type on the opposite side.

(A) Bilateral repaired separately: recurrences 9.0% (on the right 57.7% on the left 42.3%).

(B) Bilateral repaired at one operation: recurrences 8.2% (on the right 45.8% on the left 54.2%).

(C) Recurrences in bilateral hernias: 50 (right 52% left 48%). Recurrences in unilateral hernias: 70 (right 54% left 46%).

unilateral and bilateral hernias. The figures were: unilateral, right 6 per cent, left 6.8 per cent, total, right 7 per cent, left 7.5 per cent. What little difference there was favored the right side in both instances.

*Bilateral Operations*—A great deal of discussion has been held as to the advisability of performing operations for the cure of bilateral hernias of this type in one or in two stages. In a very large proportion of this group of cases, the decision as to whether the operations should be done at one or two operations was determined rather by the nature of the hernias and the difficulties encountered in doing a satisfactory repair than by the single fact that they were bilateral. That this was a logical point in making the decision is indicated by the fact that the recurrence rate was only slightly higher for bilateral hernias repaired by two operations than for those which were repaired at one time. The logical conclusion is that the recurrence rate would have been even higher for bilateral hernias repaired at two operations had they been repaired

at the same time, although this conclusion cannot be proved from the figures. That there is no greater difference in these two recurrence rates, even though the larger hernias and those with poorer tissues were included in the group done at two operations, gives sufficient grounds to draw such a conclusion.

#### INCARCERATION AND STRANGULATION

*Incidence*—These two complications were found in 78 per cent of patients with incomplete indirect inguinal hernia studied. Incarceration was present in 6 per cent and strangulation in 18 per cent.

*Recurrences*—In the absence of both of these complications the recurrence rate among patients followed for nine months or longer was 69 per cent. As compared to this figure, it was 98 per cent in the presence of incarceration and 133 per cent with strangulation.

TABLE 10—*Incarceration and Strangulation*

Strangulated or Incarcerated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	2,286	92.8	1,541	106	6.9	4 in 1,279 operations	0.31
Incarcerated*	147	6.0	102	10	9.8	2 in 81 operations	2.5
Strangulated*	44	1.8	30	4	13.2	1 in 28 operations	3.6
Totals	2,462	100.0	1,668	120	7.2	7 in 1,374 operations	0.51

\* Strangulation developed in 15 old incarcerated hernias.

*Mortality*—In 1,279 operations for repair of incomplete indirect inguinal hernias with which neither incarceration nor strangulation was present, the operative mortality was 0.31 per cent. In the presence of incarceration this figure was increased to 2.5 per cent, and in the presence of strangulation, to 3.6 per cent. That there is not more difference between these two figures is probably due to two factors: first, that the incarcerated hernias included a large proportion in which the sac was very large with many adherent structures in the contents, and, second, that in a considerable part of the strangulated hernias the strangulation fortunately had been present for a relatively short time. Also, strangulation accounted for part of the deaths of patients with incarcerated hernias.

#### RESULTS ACCORDING TO TYPE OF REPAIR

Major differences in technic only have been taken into account in the classification of these operations. Six types of repair were considered to differentiate the major variations as to operative technic and these in turn have been subdivided according to the suture used—catgut alone or a fascial suture plus catgut.



The different types of repair were as follows

*Type 1*—Repair without transplantation of the cord, with catgut sutures only

*Type 1A*—Same as type 1 except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle after the technic of McArthur

*Type 2*—Repair with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle, after the technic of Bassini, with catgut sutures only

*Type 2A*—Same as type 2 except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur

*Type 2B*—Same as type 2 except that a fascial suture from the fascia lata was used to suture the conjoined tendon to the inguinal ligament after the technic of Gallie

*Type 3*—Repair with transplantation of the cord between the overlapped layers of the external oblique aponeurosis after the technic of Willys-Andrews, with catgut sutures only

*Type 3A*—Same as type 3, with a suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur

*Type 4*—Repair with transplantation of the cord external to the external oblique aponeurosis, with or without overlapping of the aponeurosis after the technic of Halsted, with use of catgut suture material only

*Type 4A*—Same as type 4, with a fascial suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur

*Type 5*—Any of the aforementioned types of repair in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament. This included no repairs in which fascial sutures were utilized

*Type 6*—Intra-abdominal excision of the sac without repair of the inguinal rings or the inguinal canal

In a consideration of the results obtained with these various types of repair, one must bear in mind that the majority of those hernias which presented particular difficulties as to obtaining a permanent cure fell in the classifications which included either a fascial suture or a transplantation of the rectus muscle or sheath. Also, the majority of those hernias which presented the greatest probability of obtaining a permanent cure were repaired with a technic in which the cord was not transplanted

For the reasons just stated, it is not surprising that the lowest incidence of recurrences, 4.8 per cent, was found with type 1. Neither is it surprising that in this same group was found a very low incidence of infected wounds, 0.6 per cent, as it is the simplest type of operation, requiring the least manipulation and the least ligature and suture material. The number of operations of this type in which a fascial suture was used was too small for the results to have any significance.

TABLE 11—*Classification by Type of Repair*

Type of Repair*	Total Followed	Per Cent Recurrences	Per Cent Infections†	Per Cent Infections Showing Recurrences†	Recurrences	
					Indirect	Direct
1	163	4.8	0.6	100.0	62.5	37.5
1A	3	0.0	0.0			
2	972	6.8	2.3	9.1	41.0	59.0
2A	197	7.8	1.7	22.2	8.7	81.3
2B	2	50.0	0.0		0.0	100.0
3	37	8.1	5.4	0.0	100.0	0.0
3A	1	0.0	0.0			
4	179	9.2	4.0	14.3	35.7	64.3
4A	71	4.2	5.6	25.0	66.7	33.3
5	40	17.5	10.0	75.0	28.6	71.4
6	3	33.3	0.0		100.0	0.0
All repairs without fascial sutures	1,394	7.4	3.1		44.2	55.8
All repairs with fascial sutures	274	6.9	4.7		26.3	73.7
Totals	1,663	7.2	3.5	21.3	40.0	60.0

\* Type 1 Repairs without transplantation of the cord

Type 1A Repairs without transplantation of the cord. The conjoined tendon and inguinal ligament were sutured with a fascial suture from the aponeurosis of the external oblique muscle.

Type 2 Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.

Type 2B Same as type 2 with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the fascia lata.

Type 3 Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle.

Type 3A Same as type 3, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.

Type 4 Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis.

Type 4A Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle.

Type 5 Repairs in which the rectus muscle or anterior rectus sheath were sutured to the inguinal ligament.

Type 6 Repairs which consisted solely of the intra abdominal excision of the sac at the time of some other abdominal operation.

† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds which were examined in the follow up of each group.

The majority of these incomplete indirect inguinal hernias were repaired with the technic in which the cord was transplanted between the conjoined tendon and the external oblique aponeurosis (type 2). This is the typical Bassini repair. Various refinements were added in a number of cases, such as (1) careful imbrication and suture of the transversalis fascia from the pubic spine to the point of exit of the cord from the abdomen, (2) various methods of decreasing the diameter of the cord at its point of emergence from the abdomen, and (3) overlapping of the external oblique aponeurosis superficial to the cord.

Included in this group (type 2) are the general run of hernias, from which have been removed a considerable percentage of those presenting the least and greatest difficulties in obtaining a satisfactory repair. With this type of repair the incidence of recurrences, 6.8 per cent, was slightly below the average for the entire group of incomplete indirect inguinal hernias, 7.2 per cent, and, also, the incidence of infected wounds, 2.3 per cent, was less than the average for the entire group, 3.5 per cent. Postoperative infections in the incision apparently presented a smaller hazard as to the probability of recurrence than was found with most of the other types of repairs. Only 9.1 per cent of the infected wounds were found later to show recurrences.

When a fascial suture obtained from the external oblique aponeurosis was used to suture the conjoined tendon to the inguinal ligament after the technic of McArthur in this type of repair, the recurrence rate was only 7.8 per cent. This is but slightly above that found without its use. Included in this group of repairs were a great proportion of those hernias which presented major difficulties as to obtaining a satisfactory repair. It is not unexpected that this type of repair should show both an increased percentage of infected wounds, 4.7 per cent, and an increased recurrence rate in those repairs which were infected, 22.2 per cent. The number in which a suture from the fascia lata was utilized was too small to present evidence for or against the use of this technic.

In those repairs (type 3) in which the cord was transplanted between the layers of the overlapped external oblique aponeurosis after the Willys-Andrews technic, the number of patients followed was too small to yield conclusive figures. In the small group, however, both the recurrence rate, 8.1 per cent, and the proportion of infected wounds, 5.4 per cent, were greater than the corresponding figures for the Bassini type of repair. In only 1 followed case was this type of repair performed with the use of a fascial suture from the external oblique aponeurosis to unite the conjoined tendon to the inguinal ligament.

The group in which the cord was transplanted superficial to the external oblique aponeurosis (type 4) included a somewhat greater percentage of difficult repairs than did the Bassini group. Whether or not this factor was of sufficient importance to account for an increase of one third in the recurrence rate, 9.2 per cent as compared to 6.8 per cent, there is no way of proving from the information available in the various patients' charts. The difference is great enough to suggest that the Bassini type of repair gives somewhat better results.

The incidence of infected wounds, 4 per cent, and the incidence of recurrence, 14.3 per cent, after infection were both greater than the corresponding figures for the Bassini type of repair.

When the McArthur technic was added to this type of operation the recurrence rate 4.2 per cent became less than 50 per cent of that

obtained without its use and also one third less than that obtained with the Bassini type of repair. The number of patients followed was too small for these figures to be conclusive, but the data would indicate that this type of repair was satisfactory.

Although only 40 patients were followed in whom a rectus transposition (type 5) was done, the recurrence rate of 17.5 per cent showed this to have been an unsatisfactory type of repair. The large incidence of infected wounds, 10 per cent, and recurrences in 75 per cent of these infected incisions, would cause one to arrive at the same conclusion.

Intra-abdominal excision of the sac (type 6) was performed in three instances in the course of some other abdominal operation. In none of these was any attempt made to repair the inguinal canal. It is interesting to note that but 1 patient showed a recurrence in the period covered by the follow-up examinations.

The group containing all repairs in which a fascial suture was utilized was made up largely of those hernias which presented particular difficulties in obtaining a satisfactory repair. Consequently, it is most interesting that the recurrence rate, 6.9 per cent, should be the same as that observed with the Bassini type of repair, in which group a materially smaller percentage of difficult repairs was included. The incidence of infected wounds, 4.7 per cent, was twice that found in the group treated with the Bassini type of repair.

For the entire group followed, the recurrences after the repair of incomplete indirect inguinal hernias were indirect, 40 per cent, and direct, 60 per cent. The variations from these figures according to the type of repair are interesting, but the numbers of recurrences in each group were too small to justify an appraisal of each type of repair by the fact that a majority of the recurrences were either direct or indirect.

#### POSTOPERATIVE COMPLICATIONS

There were 246 postoperative complications following the 2,337 repairs, or 10.4 per cent. The recurrence rate, 8.8 per cent, in these complicated cases was slightly above the average for the entire group, 7.2 per cent.

Wound infection, which developed in 3.5 per cent of the operative wounds, was the most frequent complication (unless all respiratory complications were grouped together) and acute bronchitis the next in frequency, with an incidence of 3.2 per cent. Pneumonia, if lobar pneumonia and bronchopneumonia are grouped together, was next, with an incidence of 1.8 per cent. Pulmonary atelectasis had an incidence of 0.56 per cent and a mortality rate of 7.6 per cent. The various other (less common) complications are listed in table 12.

Respiratory complications (table 13) developed after 7.3 per cent of the operations. Of these, acute bronchitis occurred with the greatest

TABLE 12—*Postoperative Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed actively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Wound infection	82	3.5	21.2	57	12	21.3		0	0.0
2 Acute bronchitis	70	3.2	15.4	51	4	7.8	4.0	0	0.0
3 Hematomas	46	2.0	18.0	43	3	6.9	4.3	0	0.0
4 Common cold	22	0.94	16.0	8	0	0.0	0.0	0	0.0
5 Bronchopneumonia	21	0.90	18.7	13	1	7.7	0.5	1	4.76
6 Lobar pneumonia	18	0.77	22.4	12	3	25.0	11.1	2	11.1
7 Pulmonary atelectasis	13	0.53	19.5	9	1	11.1	0.0	1	7.5
A Atelectasis (right lung)	9	0.38	10.2	7	0	0.0	0.0	1	11.1
B Atelectasis (lower lobe of right lung)	3	0.13	20.5	2	1	50.0	0.0	0	0.0
C Atelectasis (left lung)	1	0.04	18.0	0	0	0.0	0.0	0	0.0
8 Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
9 Deep phlebitis	7	0.30	33.0	6	1	16.7	0.0	0	0.0
10 Pyelitis	6	0.25	20.0	6	1	16.7	13.7	0	0.0
11 Acute tonsillitis	6	0.25	12.7	3	0	0.0	0.0	0	0.0
12 Cystitis	3	0.13	18.0	2	0	0.0	0.0	0	0.0
13 Acute otitis media	3	0.13	24.3	3	0	0.0	0.0	0	0.0
14 Pleurisy with effusion	3	0.13	29.0	2	0	0.0	33.3	0	0.0
15 Epididymitis	3	0.13	19.3	3	1	33.3	0.0	0	0.0
16 Conjunctivitis	2	0.09	13.5	2	0	0.0	0.0	0	0.0
17 Delirium tremens	2	0.09	14.0	0	0	0.0	0.0	1	50.0
18 Myocardial failure	2	0.09	8.1	0	0	0.0	0.0	2	100.0
19 Chickenspox	1	0.04	11.0	1	0	0.0	0.0	0	0.0
20 Measles	1	0.04	10.0	1	0	0.0	0.0	0	0.0
21 Mumps	1	0.04	15.0	0	0	0.0	0.0	0	0.0
22 Prostatic abscess	1	0.04	63.0	1	1	100.0	0.0	0	0.0
23 Empyema	1	0.04	103.0	1	0	0.0	0.0	0	0.0
24 Psychoneurosis	1	0.04	22.0	1	0	0.0	0.0	0	0.0
25 Anxiety state	1	0.04	20.0	1	0	0.0	0.0	0	0.0
26 Toxic psychosis	1	0.04	40.0	1	0	0.0	0.0	0	0.0
27 Renal calculus (passed)	1	0.04	15.0	1	0	0.0	0.0	0	0.0
28 Uremia	1	0.04	46.0	1	0	0.0	0.0	0	0.0
29 Hemorrhage (reoperated on)	1	0.04	30.0	1	0	0.0	0.0	0	0.0
30 Cerebral hemorrhage	1	0.04	1.5	0	0	0.0	100.0	0	0.0
31 Pericarditis	1	0.04	14.0	0	0	0.0	0.0	1	100.0
32 Acute glaucoma	1	0.04	14.0	1	0	0.0	0.0	0	0.0
33 Paronucleosis	1	0.04	14.0	0	0	0.0	0.0	0	0.0
34 Peritonitis	1	0.04	15.0	1	0	0.0	0.0	0	0.0
35 Vincent's angina	1	0.04	21.0	1	0	0.0	0.0	0	0.0
36 Parietal peritoneal abscess	1	0.04	12.0	0	0	0.0	0.0	0	0.0
37 Peripharyngeal abscess	1	0.04	33.0	0	0	0.0	0.0	0	0.0
38 Pulmonary abscess	1	0.04	45.0	0	0	0.0	0.0	1	100.0
39 Fecerbarbion of hyperthyroidism	1	0.04	33.0	0	0	0.0	0.0	0	0.0
Totals	246	10.4		170	15	8.8	5.0*	7†	2.83

Five per cent of infected wounds occurred among the patients with postoperative complications (excluding those whose only complication was wound infection)

† Four patients who died postoperatively each had two complications

TABLE 13—*Postoperative Respiratory Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	75	3.2	15.4	51	4	7.8	4.0	0	0.0
2 Common cold	22	0.94	16.0	8	1	0.0	0.0	0	0.0
3 Bronchopneumonia	21	0.90	18.7	13	1	7.7	9.5	1	4.76
4 Lobar pneumonia	18	0.77	22.4	12	3	25.0	11.1	2	11.1
5 Pulmonary atelectasis	13	0.55	19.5	9	1	11.1	0.0	1	7.6
A Atelectasis (right lung)	9	0.38	19.2	7	0	0.0	0.0	1	11.1
B Atelectasis (lower lobe of right lung)	2	0.13	20.5	2	1	50.0	0.0	0	0.0
C Atelectasis (left lung)	2	0.04	18.0	0	1	25.0	0.0	0	0.0
6 Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
7 Acute tonsillitis	3	0.12	12.7	3	0	0.0	0.0	0	0.0
8 Acute otitis media	3	0.13	24.3	3	0	0.0	0.0	0	0.0
9 Pleurisy (with effusion)	3	0.13	29.0	2	0	0.0	33.3	0	0.0
10 Empyema	1	0.04	103.0	1	0	0.0	0.0	0	0.0
11 Peritonissillar abscess	1	0.04	15.0	1	0	0.0	0.0	0	0.0
12 Pulmonary abscess	1	0.04	45.0	0	0	0.0	0.0	1	100.0
13 Wound sinus, lung	1	0.04	21.0	1	0	0.0	0.0	0	0.0
Totals	171	7.3		108	10	9.2	4.7	5*	2.9

\* One patient that died had two respiratory complications

TABLE 14—*Postoperative Circulatory Complications*

Complication	Total Hernias	Per Cent of Entire Group	Average Postoperative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Hematomas	46	2.0	18.0	43	3	6.9	4.3	0	0.0
2 Pulmonary embolus	9	0.38	24.4	4	1	25.0	0.0	1	11.1
3 Deep phlebitis	7	0.30	33.0	6	0	0.0	0.0	0	0.0
4 Myocardial failure	2	0.09	8.1	0	0	0.0	0.0	2	100.0
5 Hemorrhage—patient reoperated on	1	0.04	50.0	1	0	0.0	100.0	0	0.0
6 Cerebral hemorrhage	1	0.04	1.5	0	0	0.0	0.0	1	100.0
7 Thrombosis	1	0.04	14.0	0	0	0.0	0.0	1	100.0
Totals	67	2.8		54	4	7.4	4.5	4*	6.0

\* One patient that died had two circulatory complications

frequency, 3.2 per cent. Following that came, in order, the common cold, 0.94 per cent, bronchopneumonia, 0.90 per cent, lobar pneumonia, 0.77 per cent, and pulmonary atelectasis, 0.56 per cent.

The recurrence rate for the entire group of respiratory complications was 9.2 per cent, essentially the same as that found for the total complicated cases.

Circulatory complications developed after 2.8 per cent of the operations (table 14). Hematomas, 2 per cent, pulmonary embolus, 0.38 per cent, and deep phlebitis, 0.20 per cent, accounted for the majority of these complications. The recurrence rate of 7.4 per cent was the same as for the entire group of repairs and was less than was associated with respiratory complications.

TABLE 15—Deaths (1926-1935)

Opera- tive Deaths †	Patient's Age	Hernia Strangu- lated	Duration of Strangu- lation	Resec- tion Required	Time of Death After Operation	Cause of Death
1	30	No			28 hours	Delirium tremens myocardial failure
2	42	No			2 days	Bronchopneumonia mitral stenosis
3	43	No			45 days	Atelectasis of right lung abscess of upper lobe of right lung
4	53	No			14 days	Lobar pneumonia pericarditis
5	56	Yes	4 days	No	10 days	Pulmonary infarct myocardial failure
6	63	No			36 hours	Cerebral hemorrhage
7	66	Yes	4 days	No	6 days	Lobar pneumonia
Nonoperative Deaths 1*	65	Yes	4 days	Patient moribund too ill for operation		Intestinal obstruction

\* This patient also had a hernia on the opposite side.

† Seven deaths in 1,374 operations—mortality rate 0.51 per cent.

#### OPERATIVE MORTALITY

Listed in table 15 are the postoperative deaths and 1 death of a patient with a strangulated hernia who arrived at the hospital moribund and was not operated on. The mortality figures are based on the 1,374 repairs done in the ten year period 1926 to 1935 inclusive.

The total mortality was 0.51 per cent. For hernias without incarceration or strangulation the mortality rate was 0.32 per cent, in the presence of incarceration, the rate was 2.5 per cent and with strangulation it was 3.6 per cent (table 10).

#### FOLLOW-UP DATA

Of the 2,462 patients studied 125 were not operated on, and the hernias of 2,337 were repaired by operation. Of the latter, 364 did not return for follow-up examination. Among the 1,973 who did return

for follow-up examination, 120 were found to have a recurrence. The average length of follow-up time was thirty-one months for all patients followed.

However, a follow-up period of less than nine months was considered too brief, so that for purposes of study only those patients observed over a postoperative period of nine months or longer were

TABLE 16—*Follow-up Data*

(A)					
Total number of hernias studied					2 462
Total with no operation					125
Total operations					2 337
Total operative deaths					7
Total with no follow up examination					364
Total with follow up under 9 months—no recurrence					305
Total with follow up 9 months and over (including recurrences)					1,668
Average follow up time—all cases followed 9 months and over					36 months
Total recurrences					120
Average time recurrences were first noted postoperatively					32 2 months
Percentage of recurrences with follow up of 9 months and over					7 2
Total number of operations examined postoperatively					1 973
Average follow up time for all followed cases					31 months
Total recurrences					120
Percentage of recurrences for all followed cases					6 1
Recurrences indirect, 40 per cent direct, 60 per cent					
(B)					
Length of Follow Up Time *	Total Operations Followed	Percentage of All Followed Operations	Total Recurrences Discovered	Percentage of Total Recurrences	Recurrence Percentage for Group
Under 9 months	340	17 5	35	29 7	10 3
9 months to 1 year	220	11 1	17	14 4	7 9
Under 1 year	560	28 6	52	44 1	9 5
1 to 2 years	495	24 9	27	22 9	5 0
2 to 3 years †	557	28 1	14	11 7	2 5
3 to 5 years ‡	107	5 3	6	5 1	5 7
5 to 10 years	150	7 5	13	11 0	9 0
10 to 15 years	67	3 4	5	4 2	7 6
15 to 22 years	37	1 9	3	2 5	7 5
Totals	1 973	100 0	120	100 0	6 1

\* Cases included only when the period of follow up time was ended by failure to return again for examination or by the discovery of a recurrence.

† One third of the recurrences were discovered 2 years or longer after the operation.

‡ Nearly one fourth of the recurrences were discovered 3 years or longer after the repair was done.

included in the figures throughout the study. This included 1,668 hernia repairs with an average follow-up period of thirty-six months and a recurrence rate of 7 2 per cent. The average time postoperatively at which recurrences were discovered was thirty-two and two-tenths months, with the shortest time immediately after the operation and the longest time nineteen years.

Nearly one third (29 7 per cent) of the recurrences were discovered under nine months postoperatively, 44 1 per cent in the first year, 22 9 per cent in the second year, 11 7 per cent in the third year, 5 1



per cent in the fourth and fifth years 11 per cent from the fifth to the tenth year, 4.2 per cent from the tenth to fifteenth year, and 2.5 per cent after the fifteenth year

Of the 120 recurrences following repair of incomplete indirect inguinal hernias, 40 per cent were indirect and 60 per cent were direct

#### DURATION OF POSTOPERATIVE HOSPITALIZATION

The question has often arisen as to the possibility of decreasing the incidence of recurrence following hernia repairs by increasing the duration of postoperative hospitalization. Such a procedure, if proved of value, would add little to the economic loss of wage-earning patients, as they would still return to their work in the same length of time. The added cost of hospitalization would have to be balanced against the value of the decreased liability to the development of recurrences.

Patients without complications who were kept in the hospital for more than the customary eleven to fifteen days were, in the majority of instances, patients whose hernias presented the greatest likelihood of recurrence. A certain proportion, but a much smaller one than that just under discussion, remained in the hospital for a longer period for one of the two following reasons. In the case of bilateral hernias repaired at two operations but with one admission to the hospital, the hernia repaired first automatically called for a longer postoperative hospitalization than the second repair (by between ten and fifteen days). Without taking into consideration the length of postoperative hospitalization repair of bilateral hernias in this group was followed by a recurrence rate of 9 per cent, as compared to 6.3 per cent for unilateral hernias. The second group is made up of those cases in which bilateral repair was done at one operation and some local complication developed in one repair, necessitating an increased length of hospitalization and thereby also increasing the time of hospitalization for the uncomplicated repair.

For the results to have any value in determining the effect of increased hospitalization in decreasing the recurrence rate, the complicated cases must be eliminated.

Table 17 lists the findings in this study. The last three lines give the pertinent results. The more detailed figures in the upper part of the table are given to show that the figures in the three lower divisions are not thrown off by unfair inclusions.

The number of repairs for which the patient's were hospitalized postoperatively for less than eleven days is too small for the recurrence rate to have a comparative value. They are listed separately, as it was not considered fair to include them in the list with the ordinary length of hospitalization.

The recurrence rate for the 1110 repairs without postoperative complications in which the patients were kept in the hospital for eleven to

sixteen days was 7 per cent For the 334 repairs without postoperative complications in which the patients were kept in the hospital for more than fifteen days the recurrence rate was 4.5 per cent The ordinary length of postoperative hospitalization is found to carry a recurrence expectancy 55.5 per cent greater than that noted when this period is more than fifteen days This is particularly noteworthy when one considers that this group of repairs is made up largely of hernias with which otherwise an increased incidence of recurrence would have been expected

### CONCLUSIONS AND COMMENT

1 From this study it is apparent that, to aid in keeping the recurrence rate low after operative repair of incomplete indirect inguinal

TABLE 17—*Time Patients Were Kept in the Hospital After Operative Repair*

Postoperative Time in Hospital Days	Total Operations			Without Postoperative Complications			With Postoperative Complications		
	Number Followed	Recur rences	Per Cent Recur rences	Number Followed	Recur rences	Per Cent Recur rences	Number Followed	Recur rences	Per Cent Recur rences
2 to 11	13	1	7.7	12	1	8.4	1	0	0.0
11 to 13	99	7	7.1	90	6	6.3	3	1	33.3
13	265	14	5.3	247	13	5.3	18	1	5.6*
14	580	41	7.1	538	40	7.4	42	1	2.4*
15	247	20	8.1	229	19	8.3	18	1	5.6*
16 to 22	386	30	7.8	306	14	4.6	80	16	20.0
22 and over (over 3 weeks)	78	7	9.0	28	1	3.6	50	6	12.0
Under 11	13	1	7.7	12	1	8.4	1	0	0.0
11 to 16	1,191	82	7.0	1,110	78	7.0	81	4	5.0*
More than 15	464	37	8.0	334	15	4.5	130	22	16.9
Totals	1,663	120	7.2	1,456	94	6.6	212	26	12.3

\* These patients were mostly children and the complications chiefly minor

hernias, the operations should be performed soon after the appearance of the hernia This is borne out by the figures showing an absence of recurrence in the first fifteen years of life and by a very low figure for the next ten years of life, with an increasing rate for the greater ages (tables 1, 2 and 7) Also, when the hernia was permitted to remain sufficiently long for it to become scrotal, the incidence of recurrences increased by 50 per cent, and the mortality rate became five times greater than when the hernias were smaller

2 The question as to whether bilateral hernias should be repaired at one operation or two cannot be answered conclusively by the figures shown in table 9 Since the recurrence rate for operations done in two stages was only slightly greater than that for those done at one stage, the conclusion is probably justified that the larger and more difficult bilateral hernias should be repaired in two operations This statement is made because in the cases studied this was largely done Only a

slight increase in the recurrence rate was found, although the majority of hernias operated on in two stages were certainly associated with a greater expectation of recurrence than those repaired at one operation.

However, as in deciding on the length of time a patient should be kept in the hospital after the operation, the economic factor must necessarily be taken into account. The patient's ability to pay for two periods of hospitalization instead of one and to be away from work for two periods instead of one should probably be the determining factor unless both hernias present unusual obstacles to the performance of a satisfactory repair. In this case the repairs should be performed at two operations, preferably with two separate admissions to the hospital.

For those bilateral hernias which must of necessity be repaired at one operation, an extended stay in bed will to a certain degree limit the expected increase in the recurrence rate.

3 Both incarceration and strangulation increase the expectation of recurrence by 30 to 100 per cent and give mortality rates eight and eleven times greater respectively. It is obvious that incomplete indirect inguinal hernias should be operated on early, before either of these complications develops.

4 Meticulous care should be used in the performance of the operation to prevent wound infection and hematomas, particularly since the former gives a recurrence rate three times the average for the entire group (table 12).

Pulmonary and circulatory complications can be kept at a minimum by careful administration of a properly selected anesthetic, maintenance of passive and active motion of the patient's muscles and frequent changes of the patient's position in bed postoperatively. Rigid refusal to operate on patients having even the slightest evidence of a common cold will aid materially in the reduction of respiratory complications. These points are all very important, as both the mortality rate and the recurrence rate are increased by respiratory complications, and circulatory complications increase mortality (tables 13 and 14).

5 The type of repair must be chosen for each individual hernia. There are so many factors involved that, because in a set of figures such as those given in table 11 one type of operation results in a low recurrence rate, it would be irrational to conclude that this type of repair should be applied to all hernias.

(a) These figures justify the statement that adding suture of the rectus muscle or of the anterior sheath of the rectus muscle to any type of repair of an incomplete indirect inguinal hernia is not a satisfactory procedure.

(b) Probably transplantation of the cord external to the external oblique aponeurosis does not give as satisfactory results as does the

Bassini type of transplantation. However, the possible inclusion of a greater percentage of difficult repairs in this group may have accounted for the increase in the recurrence rate of nearly 50 per cent.

(c) The figures obtained would indicate that the Willys-Andrews type of repair is an unnecessary addition to the required operative manipulation, although the number of cases in this group was too small to give definite proof.

(d) For the larger hernias, for those in patients with poor structures and when there is a definite direct weakness, the figures indicate definitely that the use of a fascial suture after the technic of McArthur gives a slightly lower recurrence rate than that observed without its use in a group of hernias in which supposedly a lower recurrence rate is more readily obtained.

6. In all cases in which the patient's financial circumstances permit, hospitalization for a minimum of sixteen days will be repaid by a decrease in the expected rate of recurrence. With hernias which are large or bilateral or which present other factors increasing the expectancy of recurrence, a minimum period of three weeks' hospitalization should be provided for.

#### REPAIR OF INCOMPLETE INDIRECT INGUINAL HERNIAS

The opinions about to be expressed are the result of the findings in this study and observations made in my own experience, combined with those points I have been able to glean from the opinions of other surgeons with more extensive experience in this type of surgical practice.

The first and most important point is that each hernia and each patient must be considered individually. The many possible combinations of the many factors involved make it impossible to outline one method of treating all hernias of this type or even a few set plans to cover this type of hernias as divided into a few broadly inclusive groups.

A few general points in the technic must be applied to all operations. Among these are careful preparation of the skin, refusal to proceed with the operation when the skin is macerated or roughened or presents any evidence of infection, clean, careful dissection with the least possible trauma to the tissues, inclusion of the least possible tissue in the clamps and ligatures when bleeding vessels are grasped, careful and complete hemostasis, so obtained that later bleeding is impossible, tying of all sutures with only sufficient tension to obtain approximation, and careful closure of the entire wound so that no dead spaces remain (and this includes avoidance of closing the wound when the edges of the skin are raised, thereby leaving air enclosed in the wound).

I am convinced from my own experience and by the figures cited by various authors that the use of fine silk for suture and ligature material throughout the operation is a valuable addition to the technic.

of hernia repair This gives a wound that heals cleanly, without reaction in or about it Silk of the finest size which will prove adequate should be used for ligatures and sutures All sutures should be interrupted The knots should be carefully placed and the ends cut as short as safety will permit

When the cord is larger than normal, it should be reduced in diameter at the point of emergence from the internal inguinal ring by incising part or all of the fibers of the cremasteric muscle In particularly difficult closures in the region of the internal ring, a worthwhile procedure is separation of the vas and the vessels of the cord so that their points of exit from between the approximated conjoined tendon and inguinal ligament are separated by two or three sutures, as described by Torek

A very important point is division of a small branch of the deep epigastric artery, which enters the cord Its division facilitates the formation of a suitably small internal ring

I am convinced that the formation of a smooth floor between the preperitoneal fat and the suture line uniting the conjoined tendon to the inguinal ligament will reduce the tendency to recurrence This is obtained by placing a row of interrupted sutures from the pubic spine to the medial side of the internal ring In the medial two thirds or three fourths of the wound this suture imbricates the loose transversalis fascia so that the inferior edge of the conjoined tendon is approximated to the shelving portion of the inguinal ligament In the upper one third or one fourth of the inguinal canal it approximates the edges of the transversalis fascia, which were opened when the branch from the deep epigastric artery was cut In this area, this fascia in addition is imbricated sufficiently to bring over the retracted inferior edge of the conjoined tendon as was done in the lower portion of the inguinal canal

The interrupted sutures approximating the conjoined tendon to the inguinal ligament are placed but not tied in turn, from below upward to the site of the internal ring The first suture is placed so that it includes the attachment of these two structures to the pubis and is introduced at right angles to their fibers Each suture is then placed sufficiently close to the one below so that adequate and close approximation will be obtained between these two structures

For several years I have made a practice of placing the highest suture (below and medial to the new internal ring) so that it includes only muscle above and below the point of exit of the cord When it is tied, the entire internal ring is made up of muscle As a result, the closure about the cord may be done firmly Since this method has been used, no recurrences at this site and no swollen testicles have been noted

One or two sutures may be placed above the internal ring but probably have no value in the ultimate outcome of the repair unless, in the operative procedure, the attachment of the internal oblique muscle and inguinal ligament was separated above the internal ring.

These sutures are then tied with only sufficient tension to approximate the conjoined tendon to the inguinal ligament.

A new external ring is formed by approximating the edges of the external oblique aponeurosis at a point below where this aponeurosis was originally incised. This point is chosen to make the size of the external ring such that it will admit the tip of the operator's little finger beside the cord. Before this first suture is tied, the cord is pulled downward until it lies in a straight line in the new inguinal canal. The remaining edges of the external oblique aponeurosis are then approximated by interrupted sutures from below upward. I have used this method of closure for several years, because it facilitates greatly the formation of the new external ring and closure of the external oblique aponeurosis.

The subcutaneous tissue is approximated by the use of interrupted sutures which include only a small bit of the cut deep fascia on each side of the incision. The skin may be closed by whatever technic the individual operator prefers, but Michel clips have given the most satisfactory scars in my experience.

As to variations from the technic which has just been described, in order to fit the needs of the different individual repairs a wide experience is of the greatest value, provided the surgeon has faced the various problems with an open mind and observed carefully the results obtained in the several manipulations with which attempts have been made to meet those problems.

Undoubtedly, if repairs without transplantation of the cord are to be done, they should be reserved for the repair of hernia in young children, in whom the internal ring is small preoperatively, the muscular and fascial structures are well developed and strong and no weakness of the posterior wall of the inguinal canal is present.

Whether or not transplantation of the cord external to the external oblique aponeurosis is a worth while procedure is at least a questionable point. It causes loss of the normal obliquity of the inguinal canal and prevents to a large degree the normal action of the abdominal muscles in protecting the inguinal area from the results of forces applied from within the abdomen. The figures in this study would at least suggest that it is a procedure which does not give added support to the repair and possibly results in a weaker inguinal region. I believe definitely that the formation of a new inguinal canal external to one of two flaps of an overlapped external oblique aponeurosis results in a weaker repair than does the Bassini repair.

In the experience at St Luke's Hospital, the use of fascial sutures in the more difficult repairs of incomplete indirect inguinal hernias appears to be a worth while procedure. Great care in the proper insertion and anchoring of this type of suture is important. Maintenance of asepsis, care in handling of tissues, hemostasis, avoidance of tension on the sutures, particular care not to damage the inguinal ligament and staggering of the successive point of entrance of the suture into and points of exit from the inguinal ligament are necessary if satisfactory results are to be obtained. I feel that it is very important to anchor each successive suture both to the conjoined tendon and to the inguinal ligament with a fine silk suture. Each fixation suture should include, in turn, a bit of the structure through which the fascial suture passes, the entire thickness of the fascial suture and again, on the opposite side, the structure through which the fascial suture passes. This effectively closes the hole made by the needle in introducing the fascial sutures at the same time that the suture is anchored.

If this fascial suture is to extend above the internal ring, it should pass the point of exit of the cord on the same side as the inguinal ligament, so that the internal ring will be made up entirely of the actual muscle of the internal oblique and transversalis muscles.

This fascial suture formed by a strip of the external oblique aponeurosis will be found satisfactory for practically all of the types of hernia under discussion. However, an occasional hernia, with an enormous internal ring with poor internal oblique and transversalis muscles or with a very wide weakened area in the posterior wall of the inguinal canal and inadequate muscles, may require for satisfactory repair the use of a fascial suture obtained from the fascia lata.

Various authors have advocated replacement of fascial sutures by a silk technic. This, in my experience, is satisfactory in some cases, but I feel that better results will be obtained by adding the use of a fascial suture to the silk technic in the more difficult repairs. Silk technic with and without fascial sutures has been used for too short a time at St Luke's Hospital for figures to be available to demonstrate by follow-up results the value of this technic and to determine whether it is advisable to give up entirely the use of fascial sutures, as has been suggested by some authors.

# CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATIONS

## II FACTORS WHICH PREDISPOSE TO CEREBRAL ANOXIA

ALBERT BEHREND, MD

AND

HELEN E RIGGS, MD

PHILADELPHIA

In a recent article<sup>1</sup> we discussed the etiologic, pathogenic and pathologic aspects of the cerebral complications of surgical operation. We have included among the cerebral complications many of the spectacular "anesthetic deaths" and postoperative hemiplegias, as well as the less spectacular but equally tragic postoperative confusional states, psychoses, prolonged comas and convulsions. In all, 21 cases of fatal cerebral complications were reported, with autopsy observations in each case.

Such cerebral complications are not, however, invariably fatal. Indeed, it seems certain that many more patients recover than die, although not all recover without residual stigmas. However, in order to establish the etiologic factors in certain types of postoperative cerebral complications it was thought imperative to use only cases in which careful postmortem examinations had been made.

Thus we have been able to demonstrate that most types of postoperative cerebral complications may occur as a result of cerebral anoxia. In the cases studied by us, anoxia was usually secondary to an acute general circulatory collapse precipitated by administration of an anesthetic plus the trauma of operation in patients whose margin of circulatory reserve had been reduced. In many cases the presence of such a preexisting chronic circulatory insufficiency was unsuspected either by the patient or his physician, but histologic observations in the vital organs were interpreted as evidence of such a disturbance.

While the cerebral changes in our cases appeared to be the result of anoxia operating through general circulatory insufficiency, it was evident that such anoxia may be produced by various mechanisms and that more than one mechanism may be present in a given case. As

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From the Department of Thoracic Surgery and the Division of Neuropathology, the Laboratories, Philadelphia General Hospital.

1 Behrend, A., and Riggs, H. E. Cerebral Complications Following Surgical Operation. I. Etiology and Pathology, *Arch Surg* 40: 24-42 (Jan) 1940.



Barcroft and others have stated there are four main types of anoxia. The first is stagnant anoxia, in which, because of slowing of the blood current, tissue asphyxia occurs. The second is anemic anoxia, which occurs when the hemoglobin content of the blood is too low to allow sufficient oxygen to be carried to the tissues. The third is histotoxic anoxia, which occurs when the cells are so damaged as to be unable to utilize oxygen. A common cause of this condition is the over-enthusiastic use of morphine, barbiturates, anesthetic drugs or alcohol. The fourth is anoxic anoxia, which may occur throughout the body as a result of an insufficiency of the available supply of inspired oxygen or locally as the sequel of trauma, acute inflammation or gas gangrene. On the basis of such physiologic concepts it is evident that anoxia plays a role in many medical and surgical conditions.

#### ORGANIC HEART DISEASE

The integrity of the brain is dependent on the efficiency of the general circulation. The cells of the brain are the most highly differentiated of the body and not only require more oxygen than do the others but are the first to show the effects of lack of oxygen. Thus, while every organ suffers under the stress of anoxia, damage to brain cells may be irreversible, and the symptoms referable to the brain are the most spectacular. It is apparent that any pathologic process affecting the heart or the blood vessels which results in a reduction of adequate blood flow to the cerebrum may contribute to the production of cerebral complications.

It would appear, then, that cardiocirculatory disorders would themselves play an important if not an essential role in predisposing to postoperative cerebral accidents. This fact we have been able to confirm. Of the 21 patients in the cases previously reported, 76 per cent showed postmortem evidence of an organic cardiocirculatory lesion existing prior to operation. It is important to emphasize that the degree of cardiac decompensation need not be severe. Nevertheless, any situation which impairs the integrity of the myocardium and the vascular system may produce a mild state of chronic tissue asphyxia. Owing to the adaptability of the organism such conditions may produce no clinical sign under ideal conditions. But when an organism so damaged is subjected to the stress of an added acute anoxia, its ability to withstand such stress may be impaired, and irreparable damage may result.

#### ANEMIAS

Severe anemias either acute (hemorrhagic) or chronic predispose to cerebral accidents. Yet it frequently becomes necessary to operate

on anemic patients. The added risks of operation in such cases can hardly be overemphasized. Chronic anemias in time produce myocardial damage. Under such circumstances, the ability of the heart to supply a sufficient blood flow to the cerebrum must be impaired. In addition, the amount of hemoglobin available to carry oxygen to the brain is materially reduced. In these circumstances the brain suffers a chronic depletion in the normally high amount of oxygen required to carry on its vital functions. While in ordinary circumstances no clinical evidence of resultant damage is apparent, chronic degenerative changes are commonly observed in the brain at postmortem examination. Under conditions requiring operation, when the blood pressure is frequently lowered, when additional blood is lost and when an anesthetic is administered which may further deplete the oxygen content of the blood, the acute changes superimposed on the preexisting chronic damage may be sufficient to cause cellular injury.

Recently our attention was called to the case of a young woman who was brought to a hospital in another city, having suffered severe loss of blood as a result of an incomplete abortion. Shortly after her admission to the hospital, curettement was performed with the patient under nitrogen monoxide and oxygen anesthesia. When the mask was removed the patient had a convulsion, and artificial respiration had to be instituted. After six weeks of vegetative existence she died of terminal bronchopneumonia. Nothing grossly abnormal was observed on examination of the brain and viscera except the aforementioned pneumonia. Microscopic examination of the brain might have revealed areas of cellular degeneration.

The dangers inherent in operating on patients with a severe degree of anemia cannot be overemphasized, and obviously the fact that the operation is of a minor nature and the anesthesia of short duration cannot minimize the danger. In a brain already suffering from relative chronic anoxia the added stress of a period of acute anoxia can produce irremediable damage, such as that which apparently occurred in the case just cited.

#### ANATOMIC FACTORS

It seems highly probable as a result of our studies that anatomic factors can influence the quantitative supply of blood to the brain and so play an important part in the production of postoperative cerebral accidents. It may be of interest to recall the work of Donaldson,<sup>3</sup> who

3 Donaldson, H. H., and Canavan, M. M. A Study of the Brains of Three Scholars, *J. Comp. Neurol.* **46** 1-95 (Aug.) 1928. Donaldson, H. H. The Brain Problem—in Relation to Weight and Form, *Am. J. Psychiat.* **12** 197-214 (Sept.) 1932.

carried out most careful postmortem studies on the brains of Sir William Osler and several other scholars and compared them with those of a group of ordinary hospital patients. After intensive study, Donaldson was forced to conclude that the only feature which distinguished genius from mediocrity anatomically was the greater vascularity of the brains in the former group.

As Riggs and Griffiths<sup>4</sup> have shown, individual variations in the pattern of the vessels which arise from the circle of Willis to supply the two halves of the cerebrum are extremely common. This may help to explain why in some cases of diffuse cerebral cellular damage in our series the clinical symptoms were referred to only one side of the brain, as was evidenced by hemiplegia. Frequently in such cases there are anomalies of the blood vessels supplying the affected side. In other words, on the side with the poorer blood supply the degree of cellular damage is greater.

#### AGE

It might be supposed that cerebral complications are most to be feared in older patients. Elderly patients with arteriosclerosis who become psychotic after an accident or an operation are common. Impaired elasticity of the blood vessels, diminution of the vessel diameter and slowing of the blood current undoubtedly contribute to the production of these complications. Yet the majority of our patients whose death could be traced most directly to cerebral anoxia were between the ages of 20 and 50 years.

One explanation may be found in the fact that the number of operations performed is much greater in the age groups between 20 and 50 years.<sup>5</sup> Furthermore, it should be recalled that the basal metabolic requirements of younger persons are greater than those of persons in the older age group. Consequently, any relative lack of oxygen will be most keenly felt by the younger persons.

#### METABOLIC DISORDERS

Cerebral complications occurring with or without operation in cases of severe hyperthyroidism are not uncommon. Several factors may combine to produce the symptoms. "Thyroid heart" and hypertension are often present. The rate of blood flow is disturbed, and the circulation time is increased, as is the demand for oxygen. Under such circumstances, not only does the brain suffer but the liver and the heart feel the effects of oxygen want.

<sup>4</sup> Riggs, H. E., and Griffiths, J. O. Relation of Anomalies of Circle of Willis to Cerebral Circulation. Preliminary Report read at the Annual Meeting of the American Association of Neuropathologists, Atlantic City, N. J., May 2, 1938.

<sup>5</sup> Berkson, J. Personal communication to the authors.

Thyroid crisis is a condition much feared and little understood. It may occur with or without operative intervention on the thyroid gland, but operation is particularly likely to precipitate it. This is readily explainable because of the additional anoxic factors introduced by the operation, namely, the administration of an anesthetic, the subsequent loss of fluid and blood and the disturbances of temperature regulation which commonly follow operation. No one has ever been able to calculate the oxygen requirements of a person in thyroid crisis, but they must indeed be enormous, and the rate of tissue catabolism must be correspondingly high. When death occurs, the usual terminal picture is marked by spectacular hyperpyrexia, the temperature in many instances reaching 108 F or more. It may be of some significance that a similar terminal hyperpyrexia is observed in some cases of so-called 'liver death' following cholecystectomy, for which no really adequate explanation has ever been offered.

It has also been our experience that in cases in which cerebral complications have developed after surgical operation the terminal temperature is similarly high in most cases in which the patients do not die immediately after the operation. Possibly the three conditions just mentioned have some connection, and at present we are undertaking clinical and experimental investigations in an effort to determine whether such a connection exists. Recent work<sup>6</sup> which indicates that toxic polypeptides absorbed in the blood stream are the cause of the so-called hepatorenal syndrome may help to throw light on the subject. Presumably, widespread tissue anoxia can cause damage sufficient to liberate such large amounts of these toxic substances that the liver and kidneys are overwhelmed in their efforts to remove them.

#### SURGICAL EMERGENCIES

Among the surgical emergencies which predispose to postoperative cerebral complications are shock, hemorrhage and overwhelming infections, such as peritonitis. It may be superfluous to emphasize at this point that in every surgical emergency each organ of the body suffers. That under some conditions the brain is the most seriously damaged organ has already been noted. Undoubtedly there are cases in which the patient is in such severe shock or is so ill at the time he is seen by the surgeon that irreparable damage has already occurred before operation is contemplated. There is, of course, little that can be done for such patients, but we are concerned here not with these but with the cases in which further damage can be prevented if the mechanism of production is better understood.

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6 St. Jacques E. The Hepatorenal Syndrome, *J Internat Coll Surgeons* 2: 295-297 (Oct.) 1939

According to Moon,<sup>7</sup> shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, by decreased cardiac output (reduced volume flow) and by increased concentration of the blood. But it matters little to which of the theories of shock one subscribes. Whatever the mechanism may be, and it doubtless varies in different cases, the result is tissue anoxia. This anoxia is probably the most important factor tending to increase or perpetuate the circulatory deficiency.

Shock is always accompanied by a fall in venous pressure, and it has frequently been noticed that the fall in venous pressure precedes the fall in arterial pressure. Weiss and his associates<sup>8</sup> have been able to show that the peripheral collapse induced by the administration of sodium nitrite with the patient in the upright position can produce a state of shock independent of any cardiac or peripheral arterial failure. The clinical importance of the venous side of the circulatory system has probably not received its just share of attention.

#### ANESTHESIA

In a previous paper we expressed the opinion that postoperative complications affecting the central nervous system might follow the use of any general anesthetic agent. Indeed, under certain conditions cerebral anoxia may occur without operation or anesthesia. Thus transient hemiplegias, confusional psychoses and even convulsions may occur in cases of cardiac decompensation, diabetic acidosis or insulin shock or during infectious diseases. We have also elsewhere warned against the injudicious use of barbiturates and opium derivatives before and after operation. Recently McClure and his associates<sup>9</sup> have substantiated the soundness of this advice by a series of investigations on experimental animals and on patients.

In the hands of most anesthetists ether probably remains the safest general anesthetic agent, yet it is not without its dangers. In experimental animals the contractility and force of the heart beat are weakened, and yet a greater output of blood is demanded by the body.<sup>10</sup> Therefore the reserve of the heart is diminished. On the other hand, when death occurs during ether anesthesia respiratory depression is usually noted

7 Moon, V. H. *Shock and Related Capillary Phenomena*. New York, Oxford University Press, 1938.

8 Weiss, S., Wilkins, R. W., and Haynes, F. W. *The Nature of Circulatory Collapse Induced by Sodium Nitrite*, *J. Clin. Investigation* **16**: 73-84 (Jan.) 1937.

9 McClure, R. D., Hartman, F. W., Schnedort, J. G., and Schelling, V. *Anoxia: Source of Possible Complications in Surgical Anesthesia*, *Ann. Surg.* **110**: 835-850 (Nov.) 1939.

10 Beecher, H. K. *The Physiology of Anesthesia*, New York, Oxford University Press, 1938.

before circulatory disturbance is clinically very marked. It is well also to bear in mind that when administering ether by the open drop method and particularly through a machine it is possible to produce a high concentration of ether in the blood to the exclusion of a sufficient amount of oxygen. It is very probable that so-called "ether convulsions" occur on the basis of an associated anoxia, although many theories have been advanced to explain such convulsions.

The great danger, of course, so far as nitrogen monoxide is concerned, is the small amount of oxygen which can be given with it while a satisfactory degree of anesthesia is maintained for prolonged operations. It was felt at one time that nitrogen monoxide was the safest of all inhalation anesthetics, but this view can no longer be held with justice. Nitrogen monoxide itself produces no direct effect either on the heart or on the medullary centers, its dangerous effects are therefore probably due almost entirely to relative anoxia.

Ethylene and cyclopropane are useful gases because of the sufficient supply of oxygen which can be given with them. However, they are inflammable and explosive. Furthermore, cyclopropane may be definitely toxic to the myocardium, as is evidenced by cardiac arrhythmias, although, experimentally, Waters and Schmidt<sup>11</sup> showed that the respiration fails before the heart fails. It is true that the depth of respiration may be greatly diminished during cyclopropane anesthesia, possibly because of the high concentration of oxygen which can be given with the anesthetic gas. This may have its advantages for the surgeon, but it is not without danger to the patient. If the depth of respiration is insufficient to effect washing out of carbon dioxide from the venous blood, a paradoxical asphyxia of the tissues can occur in the presence of an abundance of available oxygen.

Avertin with amylene hydrate is a respiratory and circulatory depressant. Its use should always be accompanied by the administration of oxygen through a mask, a catheter or an intratracheal tube. Some patients seem particularly susceptible to its action, and at present there appears to be no way of telling which patient will be seriously depressed by a dose that would have simply an analgesic effect on other patients.

Spinal anesthesia is increasing in popularity for general abdominal procedures. This increasing popularity is certainly justified. However, it should be borne in mind that spinal anesthesia can produce marked circulatory depression by paralysis of the nerves which control vasoconstriction and that the anesthetic drugs may exert their effect on vital centers if the drug reaches too high. As a result, a fall in blood pressure and slowing of the pulse are commonly seen during spinal anesthesia.

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11 Waters, R. M., and Schmidt, E. R. Cyclopropane Anesthesia, *J. A. M. A.* 103: 975-983 (Sept. 29) 1934.

The routine use of the hypodermic administration of ephedrine sulfate or of neo-synephrin hydrochloride and the intravenous administration of dextrose in 5 per cent solution may prevent the fall in blood pressure or restore it to normal levels before any serious consequences result from the relative anoxia produced by such changes

A source of possible danger in the administration of any of the various gas anesthetics is faulty apparatus. Every apparatus for administering anesthetic gases should be examined at regular and frequent intervals by a qualified expert. The dangers of using a machine with a defective valve are too great to allow this possibility to be overlooked. Such a machine may register a safe amount of oxygen flow while it is delivering an insufficient supply. Several tragic accidents have been reported as having occurred in this manner. Without doubt many more such accidents happen, although their true nature is unappreciated.

#### NUTRITIONAL DEFICIENCIES

Finally, we should be remiss if we failed to mention the role of vitamin deficiency in producing postoperative complication. The frequency of subclinical vitamin deficiencies has recently been stressed by Holman,<sup>12</sup> who showed that all patients who undergo elective operations benefit from the intensive administration of vitamins A, B, C and D for from forty-eight to seventy-two hours prior to operation and in the postoperative period.

In many cases nutritional deficiencies are sequels of organic disease, such as pyloric obstruction. Probably more frequently they are self imposed as a result of fads, diets, ignorance or economic want. In still other cases they are associated with chronic alcoholism. Whatever the underlying cause, the effect is very likely to make itself felt during the postoperative period. Vitamin B deficiencies are known to affect myocardial efficiency, and the importance of a competent myocardium has already been stressed. Vitamin C lack increases capillary permeability, which may predispose to shock. And so, in turn, the importance of an adequate blood level of each of the vitamins could be shown so far as postoperative complications are concerned.

#### CONCLUSIONS

After any presentation of the subject of cerebral complications after surgical operations, the statement is commonly made that such accidents are very uncommon. Indeed, surgeons of wide experience state that they have never seen such complications.

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<sup>12</sup> Holman E. Preoperative Precautions in the Prevention of Postoperative Pulmonary Complications. *Internat Abstr Surg* 68:335-339, 1939. *Surg Gynec & Obst*, April 1939.

It would be easier for us to believe that complications of the type we have described are seen all too frequently but that the exact nature of the complication and the manner of its production have not been fully appreciated. We have tried to emphasize that a multitude of conditions may be predisposing factors in the production of cerebral complications. Haldane<sup>13</sup> has stated that the human body is so constituted that no single organ can undergo damage save at the expense of the organism as a whole. Therefore, a seemingly unimportant disturbance of one system or one organ may assume great importance when the body is subjected to some unusual stress, such as an operation or administration of an anesthetic agent.

That many more accidents of this type occur than has been appreciated in the past has become apparent. There are many surgeons who have encountered cerebral complications following surgical operation and have been at a loss to explain them except on the grounds of cerebral embolism or thrombosis. Those careful enough to examine the brains of patients who die have frequently found that no embolism or thrombosis could be demonstrated. This left the manner of death in doubt. Such cases are rarely reported in the surgical literature, hence, recognition of this condition as a clinical entity has been slow.

Moynihan<sup>14</sup> said "Physiology, the fundamental science upon which medicine stands, is the meeting ground of physics and chemistry in their application to problems of function, both normal and aberrant, in man and animals." The influence of physiologic processes on the results of surgical operation has opened new fields for surgical investigation. In recent years much has been added to surgeons' knowledge as a result of such investigation, and the future will serve to uncover further evidence of the importance of this correlation.

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13 Haldane, J. S. *Respiration*, New Haven, Conn., Yale University Press, 1922.

14 Moynihan, B. G. A. *The Advance of Medicine*, New York, Oxford University Press, 1932.



# PREOPERATIVE DIAGNOSIS OF TORSION OF THE PEDICLE OF THE SPLEEN

REPORT OF A CASE WITH SPLENECTOMY FOLLOWED  
BY RECOVERY

C ROMITI, M D

Surgeon, Colonna House Nursing Home, Consulting Surgeon, Mackenzie  
Hospital, Demerara Bauxite Co, Honorary Consulting  
Surgeon, Colonial Hospital  
GEORGETOWN, BRITISH GUIANA

The following case is worthy of being recorded on account of its rarity and the clinical features that led to a correct preoperative diagnosis

## REPORT OF CASE

Doris D, an East Indian girl aged 16 years, was admitted to the Colonna House Nursing Home on the evening of Sept 8, 1938, with severe abdominal pain, intestinal obstruction and a visible tumor in the lower part of the abdomen

She had had an attack of fever, similar to previous known attacks of malaria, which began at midday on August 3, five days before admission. Later in the same afternoon, without any apparent cause, she felt a pain in the right iliac fossa, at first mild but quickly becoming severe. The pain soon spread all over the abdomen. At about the time of onset of the pain she noticed a mass in the lower part of the abdomen, more prominent in the hypogastric region, which had not previously been there. The bowels moved during the day.

As she lived in a distant country district (Canje, County of Berbice), no medical advice was taken, and she was treated with home remedies. On the following day (August 4), she still had slight fever and vomited any food taken. The pain was still severe, the bowels moved. On August 5 the fever and vomiting had stopped. Severe abdominal pain continued. The bowels moved twice during the day. Similar conditions held on the next day, August 6. From this day on the bowels did not act, and the abdomen began to be slightly distended. On August 7 and 8, up to the time of her admission to the nursing home, the patient continued to suffer from very severe abdominal pain, there was absolute constipation, but no vomiting or retention of urine. Her general condition had been steadily deteriorating.

In the past history there was nothing of note apart from repeated attacks of malaria over a period of years. The patient stated that for a long time she had had a large spleen, which she had been able to feel through the abdominal wall, in the left hypochondrium.

Her menstrual history had always been normal (duration, three days, cycle twenty eight days). Her last regular period had been in the last week of May 1938. She was about two and a half months pregnant. The pregnancy was the first since her marriage.

*Physical Examination*—The patient looked extremely ill. The temperature was normal, the pulse rate was 124 per minute, the respirations were rapid and shallow, numbering 28 per minute.

The general appearance was that of a well built young East Indian woman without any obvious abnormality. Although her face was drawn, she did not present the facies hippocratica. The color of the mucous membranes of the lips and tongue was normal. The conjunctivas showed no signs of anemia.

On examination of the various organs nothing unusual was found except in the breasts and in the abdomen. The breasts were well developed, the subcutaneous veins were marked, and the nipples and areolas, while they presented the appearances usually found in early pregnancy, were otherwise normal.

The abdomen was moderately and uniformly distended, no active peristaltic movements of the intestine could be seen. The lower part of the abdomen was filled by a large visible tumor its upper limit in the midline reaching as high as the umbilicus. The percussion note over the tumor was completely dull, over the rest of the abdomen it was resonant. On palpation the tumor was found to be extremely hard and showed no signs of softening or fluctuation, its surface was smooth and its edges rounded. The tumor was slightly movable from side to side, any attempt to move it up or down caused great pain.

Below the umbilicus the abdomen was tender, and palpation of the tumor was very painful. In the upper part of the abdomen there was no tenderness and even on deep palpation no muscular rigidity was elicited. There was no cutaneous hyperesthesia.

On vaginal examination the cervix was found to be soft, manipulation of the cervix did not cause pain. Although bimanual palpation of the uterus was impossible on account of the large abdominal tumor, the uterus appeared to be uniformly enlarged and soft. No resistance could be felt in the lateral fornices. The tumor appeared to rest on the fundus of the uterus but not to be attached to it. These findings were confirmed by rectal examination.

Careful examination of the left side of the hypochondrium by palpation, percussion and auscultatory percussion could not detect the presence of the spleen. The liver was normal in size and position.

The urine was free of albumin and sugar. There was no sediment on microscopic examination.

*Differential Diagnosis*—The onset of the disease, with sudden pain in the right lower quadrant of the abdomen, was suggestive of acute appendicitis. This was easily excluded by the hypogastric tumor and by the clinical course of the disease during the five days before admission. In view of the two and a half months of amenorrhea, ectopic gestation had to be considered. This also appeared to be ruled out, there had been no vaginal bleeding at any time, and there were no signs of internal hemorrhage, the mass felt in the lower part of the abdomen was too uniform in contour and too solid to be a hematocele. On vaginal examination there was no tenderness of the cervix, there was no mass in either fornix, and the tumor appeared to be resting on the uterus, which was enlarged to the size usual with ten weeks' pregnancy.

The only diagnosis that could explain the symptoms and the clinical course of this acute abdominal condition appeared to be torsion of a mobile abdominal tumor on its pedicle. This involved consideration of the following possibilities: (1) a solid mesenteric tumor, (2) an ovarian cyst or tumor, (3) a pedunculated subserous fibroid, and (4) a prolapsed spleen.

Any one of these conditions, once torsion has taken place, can give rise to a similar clinical picture. The presence of a pedunculated subserous fibroid was

very improbable, as, apart from the youth of the patient, fibroids, while extremely common in Negroes, are exceptional in East Indians. In arriving at a differential diagnosis of the tumor, the only indications it was possible to consider were the symptoms caused by the presence of such a large mass in the abdomen before torsion took place. It was quite unlikely that such a mass should have existed unnoticed in the abdomen before onset of the acute condition.

The patient stated that she had never observed any tumor in the lower part of the abdomen before her present illness. But she was positive that she had long been subject to recurrent attacks of malaria and that she had a large spleen. Moreover, she lived in a highly malarial district, where the splenic index among East Indians is high. The tumor had the shape, size and consistency of an enlarged spleen, and careful examination of the left side of the hypochondrium could not detect the presence of this organ in its normal position.

It is pertinent to point out here that prolapse of the spleen, with or without torsion, is not as uncommon in this colony as in nonmalarial countries. If torsion of the pedicle is present the condition may give rise either to acute or to chronic symptoms. In the ordinary case of prolapsed spleen seen in this colony the spleen descends vertically, and the lower pole is found resting in the left iliac fossa, whereas when the spleen is merely greatly enlarged but not prolapsed the lower pole will be found at the umbilicus or stretching across into the right iliac fossa.

A diagnosis was therefore made of torsion of a suddenly prolapsed malarial spleen.

*Operation*—On August 9, operation was performed with the use of spinal anesthesia. The abdomen was opened through a left paramedian incision extending from the hypogastrium to above the umbilicus. As was expected, when the peritoneum was opened a large spleen was found lying in the pelvis, its long axis lay transversely with the upper pole on the right side. The external and posterior surfaces looked upward and reached the level of the umbilicus. Some recent fibrinous adhesions between the spleen and the omentum, the transverse colon and loops of the small intestine were easily stripped off without any bleeding. A small quantity of free clear fluid in the lower part of the abdominal cavity was dried out with sponges. The large intestine was somewhat distended and hyperemic, once it had been freed from the adhesions, gas and feces were passed per anum (an event expedited by the spinal anesthesia), and the distention subsided.

There was no difficulty whatever in delivering the spleen through the wound as the pedicle was greatly elongated. The pedicle had been completely twisted twice on its axis. The spleen, in addition to the enlargement due to malaria, was engorged with blood. The vessels in the pedicle were thrombosed, particularly noticeable was a large vein, distended and thrombosed which pursued a serpiginous course between the layers of the gastrosplenic ligament, which was itself much stretched and elongated. There was a large, already clotted subcapsular hemorrhage at the hilus of the spleen.

The pedicle of the spleen, being wide and thick was ligated and divided in sections, each section being secured by two ligatures, and the spleen was removed. The large thrombosed vein was also removed, together with part of the gastrosplenic ligament.

The size and appearance of the uterus were those associated with ten weeks pregnancy, the organ was otherwise normal, and there were no adhesions between it and the spleen. After careful examination of the entire abdominal cavity the abdomen was closed without drainage. The operation lasted approximately twenty-five minutes, the general condition of the patient was good.

The postoperative course was uneventful apart from two not unexpected incidents. One hour after the operation the patient had an attack of malarial fever, which reacted to 15 grains (0.97 Gm.) of quinine bishydrochloride given intramuscularly. She aborted on the eighth day after operation. She was discharged cured sixteen days after the operation.

*Pathologic Picture*—The spleen weighed 2 pounds and 2 ounces (963 Gm.) The thrombosed vein in the gastrosplenic ligament, without untwisting its spirals, was 11 inches (28 cm.) long and  $\frac{1}{3}$  inch (0.8 cm.) in diameter. The main points



Fig. 1—Lateral view of the spleen. Note the thrombus emerging from the sectioned splenic vein.

of note in the organ removed were (1) the complete double rotation of the pedicle on its axis, (2) the subcapsular hemorrhage at the hilum, and (3) the extensive thrombosis of the vein in the gastrosplenic ligament.

No microscopic sections were made.

#### COMMENT

Rotation of the spleen on its pedicle is a very rare occurrence. The symptoms of the condition are such that the preoperative diagnosis is that of acute peritonitis, acute intestinal obstruction or, more commonly,

owing to the presence of a tumor lying in the pelvis, torsion of the pedicle of an ovarian cyst

Torsion of the pedicle of the spleen is considered to be a complication of a wandering spleen. This condition occurs more frequently in women than in men, and its causes must be sought in some alteration of the peritoneal folds that form the suspensory ligaments of the spleen. Such an alteration may be due to a congenital elongation or to an



Fig 2—Spleen viewed from the hilus. Note the double torsion of the pedicle

acquired one. An acquired elongation may result either from rupture of the peritoneal folds or from dragging on the folds from enlargement of the spleen. Repeated pregnancies are considered to be an etiologic factor in so far as they conduce to general visceroptosis and therefore to ptosis of the spleen.

The case described here is of particular interest on account of the youth of the patient, she was strong and well built, without any weakness of the abdominal wall. One etiologic factor appears to have been enlargement of the spleen due to malaria. There is no obvious reason

why the spleen should suddenly have prolapsed into the pelvis, rotating twice on its pedicle in its descent. It is suggested that the acute attack of malaria at the onset caused acute congestion of the spleen and an increase in the already abnormal weight of that organ and that the splenic ligaments, already elongated from either congenital or acquired causes, were unable to sustain the weight of the spleen.

Darfeuille<sup>1</sup> stated that the splenic ligaments cannot sustain a weight greater than 2.5 Kg. In this case the weight of the spleen removed

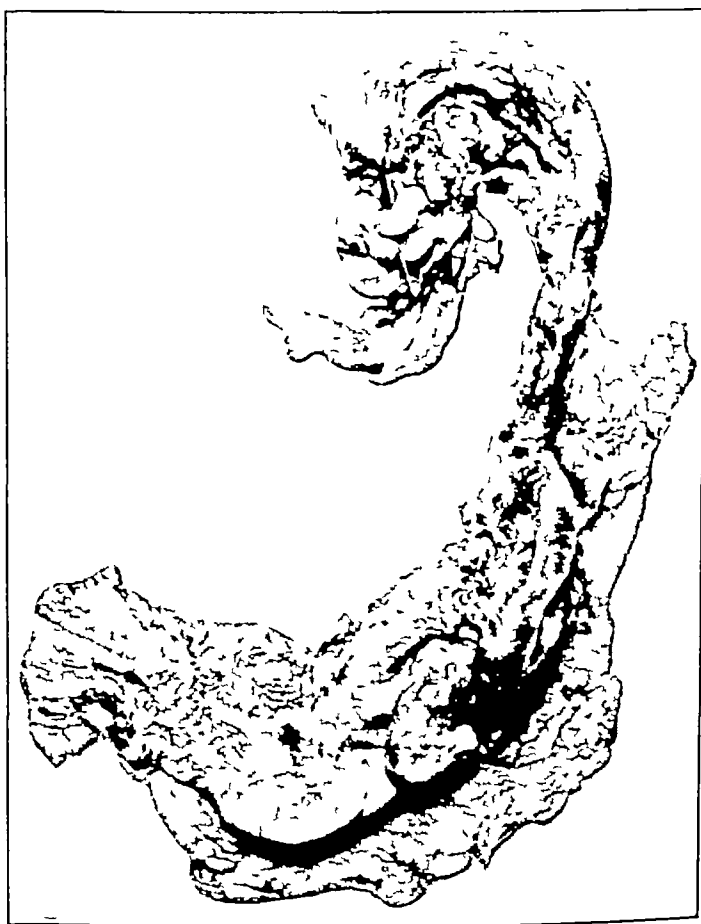


Fig. 3—Thrombosis of the splenic vein

was 2 pounds and 2 ounces, less than half the weight quoted from Darfeuille. However, it is possible that when the ligaments of the spleen are stretched and elongated, as they were in this case, they may be able to sustain a lesser weight than is normal. No sign of laceration of the ligaments was observed at operation.

<sup>1</sup> Darfeuille, C. *Deplacements de la rate avec torsion du pedicule*, Thesis, Paris, no. 3, 1894.

During the descent of the spleen into the pelvis, as described by Childe,<sup>2</sup> the upper pole, on account of its greater size and the normally oblique position occupied by the spleen in the left hypochondrium, is the first to tip forward toward the midline, thereby causing rotation of the pedicle from left to right. The farther the upper pole descends, the greater will be the torsion of the pedicle. Once the spleen has lost its normal position and lies free in the abdominal cavity, peristaltic movements of the intestines may cause further rotation.

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<sup>2</sup> Childe, C. P. Wandering Spleen. Haemorrhage Within the Capsule, Splenectomy, Recovery. *Brit. M. J.* **2**: 1631, 1903.

# SEVENTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G KUHNS, M D

ROBERT J JOPLIN, M D

WILLIAM A ELLISTON, F R C S

GEORGE BAILEY, M D

AND

JOHN A REIDY, M D

BOSTON

JOSEPH E MILGRAM, M D

NEW YORK

FREDERICK E ILFELD, M D

LOS ANGELES

AND

ROBERT PERLMAN, M D

CINCINNATI

## CONGENITAL DEFORMITIES

*Congenital Bowing and Pseudarthrosis of the Lower Part of the Leg*—Pseudarthrosis following fracture or osteoclasia during childhood in cases of congenital bowing of the lower part of the leg has been observed frequently, but its association with von Recklinghausen's neurofibromatosis has not been reported in the English literature Barber<sup>1</sup> reports 5 cases, in 4 of which there was definite bending of the lower part of the leg present at birth In 1 case, fracture and operative intervention were avoided, with the result that no functional handicap now exists In fact, some improvement in the degree of angulation took place with growth Osteotomy, osteoclasia and fracture were each followed by pseudarthrosis in 3 cases In 1 case in which no history of bending could be obtained, pseudarthrosis followed fracture In all of these cases typical lesions of von Recklinghausen's disease were present

*Frequency of Congenital Deformities in Families*—An editorial in *The Journal of the American Medical Association*<sup>2</sup> reviews a study by

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This report of progress in orthopedic surgery is based on a review of 116 articles selected from 138 titles pertaining to orthopedic surgery and appearing in the medical literature approximately between Nov 1, 1939, and March 1, 1940

<sup>1</sup> Barber, C G Surg, Gynec & Obst 69 618, 1939

<sup>2</sup> Frequency of Congenital Malformations in Families, editorial, J A M A.



Murphy of statistics in Philadelphia for a period of five years. It was found that gross congenital malformations afflict 1 of every 213 persons who are born alive. The rate is twice as high among white persons as among Negroes. The frequency of birth of subsequent malformed offspring was twenty-five times greater in families already possessing a malformed child than in the general population. The investigations lead to the conclusion that gross congenital malformations arise solely from influences which affect the germ cells prior to fertilization. No relation was demonstrated between frequency of malformation and such factors as illegitimacy, economic or social status or chronic disease at the time of conception.

[ED NOTE Earlier studies were reviewed in previous reports of progress.]

*Muscular and Skeletal Changes in Arachnodactyly*—The syndrome arachnodactyly (spider digits) is discussed in detail, and 6 cases illustrating various features of the syndrome are reported<sup>3</sup>. The cause of the condition is obscure, but there is a family history of the lesion in over half of the cases reported. The abnormalities associated with arachnodactyly are not ordinarily detected until the second or third year of life. In all cases there is a decrease of soft tissue in some portion of the body and hence an actual or apparent lengthening of the hands and feet, particularly the fingers and toes. The face may have an appearance of maturity because of a decrease of subcutaneous tissue. Muscular weakness is proportional to the size of the underdeveloped muscles. Microscopic examination of muscle from 2 patients showed normal muscular tissue. Ligamentous relaxation is always present and is usually most pronounced in the joints of the hands and feet. Subluxation of the sternoclavicular joint and dislocation of the patella have been reported. When contractures occur, the fingers and toes are usually involved, but occasionally only the larger joints are affected. Persons with arachnodactyly usually have contractures, but occasionally only the larger joints are affected. Persons with arachnodactyly are usually taller than normal persons and weigh less. They commonly have a spinal deformity, scoliosis, kyphosis or kyphoscoliosis, which appears in early life and slowly progresses but in most cases does not become severe. Dolichocephalus, prognathism, a narrow-arched palate and asymmetry of the skull are common anomalies. Heart disease, usually on a congenital basis, is a frequent accompaniment of the disease. The ophthalmologic features are those associated with ectopia lentis, iridodonesis, contracted pupils and irregularity of the anterior chamber of the eye. Bilateral dislocation of the lenses is an outstanding symptom. Improvement of vision

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<sup>3</sup> Fahy, J. J. Muscular and Skeletal Changes in Arachnodactyly, Arch Surg 39:741 (Nov.) 1939.

usually results from removal of the lens in cases in which it is completely dislocated. Pain in the foot may necessitate the use of supports. Contracture of the fingers may be treated with improvement in function.

[ED NOTE: There are wide variations in the amount of deformity presented. Many patients show the changes only in the hands and feet.]

#### DEVELOPMENTAL DISEASES

*Epiphysitis of the Spine*—Nathan and Kuhns<sup>4</sup> feel that this condition is a relatively common lesion. Sixty-nine of the 75 cases studied were observed during the past six years. Most of the patients visited the hospital for the treatment of faulty posture. The roentgen studies revealed irregularity of the upper and lower surfaces of the vertebral bodies to be the most constant finding. The late changes were constantly found to consist of anterior wedging of the vertebral bodies. Under treatment the deformity was decreased but rarely corrected. Deformity was prevented in only 2 cases. Treatment usually consisted of application of a plaster jacket with the spine in extension, in addition, corrective exercises were given. In the early acute stages of the disease, recumbency in a plaster shell with the spine in extension, which was carried out in only 5 cases, seemed to be the most efficient form of treatment. In adult patients who had had no previous treatment, severe deformity associated with pain and weakness in the back was usually present.

*Late Impairment of the Spinal Cord in Scheuermann's Juvenile Kyphosis (Spinal Epiphysitis)*—Wretblad<sup>5</sup> reports on 6 patients, all young men engaged in hard physical labor, who had juvenile kyphosis. In these patients symptoms of medullary irritation and compression developed. As a rule the symptoms appeared first on one side and later on the other. Numbness, weakness and unsteadiness in the legs were observed. Spastic paralysis of the legs was present in several cases. Myelographic study revealed a block at the apex of the curve. Laminectomy led to improvement in 3 patients whose symptoms had been of short duration. Another, in whom symptoms had been present several years, died after laminectomy. In this case autopsy showed that irreparable damage had occurred to the spinal cord.

*Pectus Excavatum*—Brown<sup>6</sup> states that pectus excavatum is characterized by a funnel-shaped depression of the sternum, the apex of which is located at the junction of the xiphoid process with the gladiolus. Prevention or correction of this deformity is indicated because of definite functional restrictions on the circulatory and respiratory mechanisms and, in women, for esthetic purposes. The diaphragm is the chief

4 Nathan, L., and Kuhns, J. G. *J. Bone & Joint Surg.* **22**: 55, 1940.

5 Wretblad, G. *Acta psychiat. et neurol.* **14**: 617, 1939.

6 Brown, A. L. *J. Thoracic Surg.* **9**: 164, 1939.

deforming factor, since, with its attachment to the lower part of the sternum, it is the only muscular force capable of drawing the sternum inward with the point of maximum indentation at the sternoxiphoid junction. A strong factor in maintaining deformity is the substernal ligament, which is continuous with the linea alba in the abdomen. The heart may be fixed in the midline, resulting in encroachment and cardiac embarrassment, or it may be displaced to the right or to the left, with no resulting disturbance. There is a strong hereditary factor in this deformity. Treatment for the adult consists of elevation of the depressed portions of the sternum, cartilages and ribs to correct the obvious skeletal deformity. However, the contracted and depressed substernal ligament must also be sectioned to allow for extension of the chest on the abdomen and for correction of the round-shouldered habitus. In early childhood the simple procedure of section of the substernal ligament and freeing of the sternal attachment of the diaphragm is sufficient to prevent full development of the deformity.

[ED NOTE In children, improvement in this condition is observed with respiratory exercises. The editors have had no experience with operative section of the substernal ligament.]

#### NUTRITIONAL DISTURBANCES OF BONE

*Osseous Dystrophy Following Severe Icterus Neonatorum*—Braid<sup>7</sup> reports the cases of 2 patients with severe jaundice at birth who showed osseous dystrophy, pathologic pigmentation of the skin and sexual precociousness. The author believes that damage occurs to the liver, interfering with the storage and utilization of vitamins. The first patient, a youth of 19, had had bony deformity since the age of 2. There were kyphosis, deformity of the chest and deformity of the leg. Laboratory studies carried over a number of years showed a relatively low level of blood calcium. Biopsy showed irregular trabeculation of the bones, with vascular fibrous tissue in the interstices resembling osteitis. The roentgenograms showed cystic changes at the ends of the diaphyses with numerous old fractures. The second patient was a girl aged 2 years. The osseous appearance was similar to that in the first case.

*Osteomalacia of the Spinal Column from Deficient Diet or from Disease of the Digestive Tract*—Meulengracht<sup>8</sup> records the cases of 6 patients living in Denmark in whom osteomalacia of the spinal column developed as the result of deficient diet or after gastrointestinal disease. There were 4 others who had the same condition from an excessive use of laxatives. From his studies the author feels that the diet of the adult population is deficient in calcium and in vitamin D. All of

7 Braid, F. Arch Dis Childhood **14** 181 1939

8. Meulengracht E. Acta med Scandinav **101** 138 1939

these patients were past middle age. Treatment consisted of support to the back and the addition of vitamin D and calcium to the diet.

#### TUBERCULOSIS

*Extra-Articular Foci in Tuberculous Arthritis*—Fifty-five cases of extra-articular tuberculosis of the hip joint in children are reviewed by Cholmeley.<sup>9</sup> The commonest sites were in the medial half of the acetabular roof (19 cases) and in the femoral neck (17 cases). Twelve children were treated by excision of the focus or by curettage, the remaining 43 were treated purely conservatively. Of these 43, only 3 escaped involvement of the hip joint (7 per cent), of the 12 operated on, only 1 (8.3 per cent) escaped involvement. The average time that elapsed before involvement of the hip could be demonstrated was about seventeen months in each series. It is concluded that less than 10 per cent of children with extra-articular foci around the hip recover with an intact hip joint.

*Pott's Disease in Children*—Smith<sup>10</sup> reports an analysis of 81 cases of tuberculosis of the spine treated in Sydney, Australia. Of the 81 patients, 17 could not be traced. Fifteen had been recently observed, 12 had died, and 2 were cured. There were 7 who were almost without symptoms but could not do all of their usual activities. Their condition was called insecure fibrous union. There were 18 in whom the disease was still active or had become active again. Spinal fusion was performed on 10. In 6 of these abscesses developed after operation, 5 suffered from an increase of the deformity, and 2 became paraplegic. The author states that stabilizing operations are contraindicated for children with active disease and that stability of the kyphos is dependent on vertebral contact.

[ED NOTE: This gloomy view of the ineffectiveness of spinal fusion is not held in America. The recent report of Swett suggests that complete healing occurs only in the presence of vertebral contact.]

*Tuberculous Spondylitis*—Walheim<sup>11</sup> studied 221 cases of tuberculosis of the spine in children observed at St. Gorans Hospital, Stockholm. One hundred and forty-nine children were treated operatively (method of Albee). Fifty per cent of the children were under 10 years of age. Two or more vertebrae were involved in 90 per cent of the cases. Gibbus was found in over 90 per cent of the patients. Abscesses were found in 60 per cent, and fistulas, in 25 per cent. Paralysis occurred in 6 per cent. Death occurred in 60 cases, in 31 from spondylitis directly, in 20, from other types of tuberculosis, and in 9, from non-

9 Cholmeley, J. A. *Brit J Surg* **27** 224, 1939.

10 Smith, G. K. M. *J Australia* **2** 303, 1939.

11 Walheim, T. *Acta chir Scandinav* **83** 123, 1939.

tuberculous diseases Of these 123 living operatively treated patients, 91 are entirely well, 18 have slight trouble with their backs, and 1 is unable to work Of the 34 living conservatively treated patients, 25 are well, 8 have slight trouble with their backs, and 1 is unable to work The functional ability is distinctly better in the backs of the patients operated on The time spent at the hospital was longer for those operated on The active disease lasted longer in those conservatively treated A greater tendency to recurrence of the disease was observed in the conservatively treated patients

#### SYPHILIS

*Syphilis of the Skeleton in Early Infancy*—Caffey<sup>12</sup> studied roentgenograms of the skeletons of 550 young infants who did not have syphilis In 22 cases the roentgenograms showed changes indistinguishable from syphilitic osteochondritis, osteoperiostitis and osteomyelitis Caffey concludes that the roentgen findings in the skeleton per se are not conclusively diagnostic of early infantile syphilis

#### GONOCOCCIC ARTHRITIS

*Gonococcic Arthritis in the Newborn*—Parrish, Console and Battaglia<sup>13</sup> present a case of gonococcic arthritis in a newborn Negro treated with sulfanilamide The mother had migratory articular pains one week before delivery and a profuse vaginal discharge at the time of delivery When the child, a boy, was 3½ weeks old, he was brought to the hospital with a swollen, warm, tender, flexed left knee Aspiration showed thick pus, from which gonococci were cultured Sulfanilamide was given, and the swelling, pain and tenderness diminished by the fourteenth day in the hospital but recurred when the drug was withdrawn Therapy was again instituted, and the swelling subsided in four days and did not recur when the drug was discontinued A short review of the literature, showing the frequency of this disease in the newborn, is presented

#### BACK

*Sacroiliac Changes in the Diagnosis of Spondylarthritis in the Early Stages*—In an examination of 153 cases of ankylosing spondylarthritis, Forestier<sup>14</sup> found that the sacroiliac joints were involved in 98 per cent In 12 instances observed in the early stages of the disease he found the sacroiliac joints roentgenographically involved prior to any changes in the spine The reverse was not observed Hence the author emphasizes the importance of sacroiliac changes in the early diagnosis of

12 Caffey, J. *Am J Roentgenol* **42** 637, 1939

13 Parrish P P, Console W A and Battaglia J. *Gonococcic Arthritis of Newborn Treated with Sulfanilamide* *J A M A* **114** 241 (Jan 20) 1940

14 Forestier, J. *Radiology* **33** 369, 1939

ankylosing spondylarthritis. These changes consist of marginal decalcification followed by a spotted, mottled appearance of the cancellous bone and later by loss of joint space and synostosis.

*Intraspinal Lesions Associated with Pain Low in the Back and Sciatic Pain*—Camp and Addington<sup>15</sup> report their observations based on 417 cases in which iodized poppyseed oil was injected into the spinal subarachnoid space for the purpose of localizing a suspected lesion affecting the spinal cord or the cauda equina. In 283 of these cases (67.9 per cent) subsequent laminectomy was performed. The positive diagnoses were as follows: tumor of the cord, 45 cases; protruded intervertebral disk, 208 cases; hypertrophied ligamentum flavum without protrusion of the disk, 6 cases; and miscellaneous conditions, 32 cases. The examination was reported giving negative results in 126 cases, or 30 per cent. Thirteen of the patients were operated on in spite of the negative results. A protruded disk was found in 7 of these cases, hypertrophy of the ligamentum flavum in 4 and no lesion in 8. The authors express the belief that iodized poppyseed oil gives more accurate results than does air, that it will reveal certain structures not seen with air and that it has localized lesions that air has failed to disclose.

*Air Myelography in the Diagnosis of Intraspinal Lesions*—Chamberlain and Young<sup>16</sup> report their experience with air or oxygen myelography in over 150 cases of pain low in the back or sciatic pain. In over half of these cases the lumbocaudal sac was studied. There were positive findings in this region after injection of air in 10 patients. All of these came to operation, and in each the uncovered lesion was at the exact level demonstrated by the roentgenograms. From 30 to 50 cc of air was used to fill the lumbocaudal sac in adults. When the Queckenstedt test shows either complete or partial block, 4 to 6 cc of air is injected below the suspected lesion, and stereoroentgenograms are taken with the patient in the upright position. The authors demonstrated complete block in the lumbocaudal sac in 3 patients, 2 of these had tumors, and 1 showed herniated cartilaginous disk.

*Neurologic Aspects of Herniated Nucleus Pulposus*—Spurling and Bradford,<sup>17</sup> on the basis of 85 low intraspinal lesions treated surgically, present what they have found to be a characteristic clinical picture of herniated nucleus pulposus at the fourth and fifth lumbar interspaces. Briefly, the symptoms and signs include severe, persistent sciatic pain, paresthesias (which are far more localizing than is the distribution of

15 Camp, J. D., and Addington, E. A. *Radiology* **33**: 701, 1939.

16 Chamberlain, W. E., and Young, B. R. *Radiology* **33**: 695, 1939.

17 Spurling, R. G., and Bradford, F. K. *Neurologic Aspects of Herniated Nucleus Pulposus at Fourth and Fifth Lumbar Interspaces*, *J. A. M. A.* **113**: 2019 (Dec. 2) 1939.

the pain), stiffness of the lumbar part of the spine, a positive Lasegue sign, hyperesthesia of the foot and of the lateral aspect of the leg and diminution or absence of the ankle jerk. They feel that a more thorough experience with the neurologic picture has made possible accurate diagnosis from clinical evidence alone in the majority of instances. These signs are not peculiar to this entity, since neoplasms along the course of the sciatic nerve, pelvic and rectal disease and disease of the osseous structures may simulate the clinical picture.

*Sciatic Radiation of Pain Low in the Back*—Steindler<sup>18</sup> attempts to explain the lesion in cases of low back pain on an anatomic basis. This is possible because there exists in cases of pain low in the back a so-called trigger point. For example, in cases of the lumbosacral syndrome this point exists at the lumbosacral junction, in cases of the tensor fasciae latae syndrome the tender point is at the lateral border of the fascia and iliotibial band, with a positive Ober sign. The author states that sciatic radiation of pain in a large group of cases has nothing whatever to do with direct irritation either of the nerve trunk or of its roots but is purely a reflex phenomenon which follows, instead of preceding, pain in the lower part of the back. Furthermore, it is the author's belief that the afferent branch of the reflex arc is furnished by the sensory fibers supplying the injured muscular and aponeurotic structures and that the connection with the sciatic nerve is made not lower than the spinal ganglion and possibly in the spinal cord. To prove the reflex character of this radiation, the author first shows that anatomically the territory involved is entirely separate from the origin of the sciatic nerve. The proof which establishes the causal connection between the local lesion and the sciatic radiation rests on the fact that irritation of the so-called trigger point exaggerates the sciatic radiation, whereas injection of procaine hydrochloride at this point reduces the local pain as well as the sciatic irritation. In 100 cases the author, with the assistance of Dr J. V. Luck, found that the test gave a positive result in 69 and a negative result in 31. Of the 69 cases in which it gave a positive result, the end results were good in 84 per cent and poor in 16 per cent, whereas of the 31 cases in which the result was negative, the end results were good in 20 per cent and poor in 80 per cent. The authors feel that in a considerable proportion of cases of radiating pain low in the back recognition of the reflex character of the radiation of pain is essential to rational diagnosis and treatment of the condition.

*Spondylolisthesis*—Hitchcock<sup>19</sup> presents 3 cases of spondylolisthesis, with roentgenograms and case histories. Roentgen evidence of progressive slipping of the fifth lumbar vertebra on the sacrum is presented

18 Steindler, A. J. Bone & Joint Surg. **22**: 28, 1940.

19 Hitchcock, H. H. J. Bone & Joint Surg. **22**: 1, 1940.

In trying to explain the cause of this condition the author states that trauma during delivery or shortly after may be the cause of this defect. His belief is based on observations made on stillborn infants, on whom he was able to demonstrate fractures of the neural arch in the lumbar region by hyperflexion, such as might occur during labor or delivery whereas hyperextension did not result in a fracture of the neural arch. Furthermore, the author cites studies by Willis, Hayek and others, who failed to find, in spite of deliberate search, a single example of separation either of anomalous centers of ossification or imperfect ossification which would correspond with such a defect in the neural arch. This study was based on a collection by the various authors mentioned of over 2,000 spines. Spondylolisthesis therefore appears to be the result of trauma rather than of congenital defects.

*Scoliosis Following Empyema*—Scoliosis resulting from pulmonary disease is usually of one of two types.<sup>20</sup> 1. Scoliosis following empyema—the concavity is toward the empyema, and there is little or no rotation of vertebral bodies. 2. Scoliosis complicating thoracoplasty—the convexity is toward the resected ribs. In a survey of 65 cases of empyema operated on in the years 1932 to 1936 inclusive at Mount Sinai Hospital, New York, none of 52 patients with acute empyema whose wounds healed permanently in a mean time of four months or less had persistent scoliosis. Of 13 patients with chronic empyema requiring multiple operations, rib resections and excisions of the soft parts, persistent scoliosis developed in 5. These 5 were 12 years old or under, and only 2 showed scoliosis so marked as not to be hidden by clothing. These 2 are discussed in detail. The most severe scoliosis was a 97 degree curve, which followed a thoracoplasty at the age of 12 years for chronic empyema. The scoliosis was of the usual thoracoplasty pattern, with the convexity on the side of operation and with considerable rotation of the vertebral bodies. Treatment with various types of jackets was of no avail. In the other case, severe scoliosis followed chronic empyema for which operation was first performed at 2 years of age. The curvature progressed in spite of treatment. The curve was of the postempyemic type, with the concavity toward the diseased side and without rotation.

#### NEOPLASMS

*Multiple Myeloma*—This disease, a multiple neoplastic disease of bone marrow or a diffuse hyperplasia, usually of cells resembling plasma cells, is discussed by Ulrich.<sup>21</sup> In 259 case histories of multiple myeloma it was found that absence of pain was rare (4 per cent). Roentgen

20 Selig, S., and Arnheim, E. Scoliosis Following Empyema, Arch Surg 39 789 (Nov.) 1939

21 Ulrich, H. Multiple Myeloma, Arch Int Med 64 994 (Nov.) 1939



evidence of tumor was present in 96.9 per cent. Bence Jones protein was absent in 38.2 per cent. Bence Jones protein is not a single substance but rather a group of similar, but not identical, proteins, and this complexity may have a bearing on the difficulties of determining its presence under certain circumstances. The effect of this disease on the kidneys is to produce obstruction of the tubules by formation of tubular casts of Bence Jones protein. Extraosseous myeloma is not uncommon. The four possibilities of origin are by direct extension from intraosseous tumor, by metastasis, by independent development and by growth of a primary extramedullary tumor. Direct extension and metastasis are the most common sources. The nature of myeloma cells has been much disputed. In most cases the cells resemble plasma cells more closely than any other known form of cell. There are, however, frequent variations. The origin of all of these different types of cells is probably from a single type of myeloid cell. In its relation to leukemia, multiple myeloma is a neoplastic disease occupying a position midway between frank tumors and diffuse leukemic hyperplasia. The author reports 1 case with certain noteworthy features, consisting of tumors in the testes, absence of pain, absence of roentgen evidence of abnormality in the bones and the presence of myeloma cells in the circulating blood.

Eighty-six cases studied by Ghormley and Pollock -- were divided into 5 groups, as follows. Group A 19 cases in which the diagnosis was proved by postmortem examination. Group B 53 cases in which the diagnosis was made on a basis of clinical and roentgen findings (all of the patients in groups A and B have died). Group C 5 cases in which the diagnosis was made on clinical and roentgen evidence. No follow-up record had been received from the patients in this group, though it is assumed that they were dead. Group D The patients in this group, proved by biopsy to have multiple myeloma, are still alive. Group E 3 patients still alive one year or more after the original diagnosis was made. The diagnosis here was made on the basis of clinical and roentgen findings. A detailed study of the cases of group D is appended. The average duration of the disease in all cases was twenty-six and nine-tenths months, in the proved case, twenty-six and eight-tenths months. Bence Jones proteinuria was present in only 51 per cent of the entire group. The albumin-globulin ratio was reversed in only 50 per cent of the cases and in the series of proved cases none of these reactions were positive. The same may be said of the reactions for calcium phosphorus phosphatase and the determinations of basophilia or eosinophilia. Regarding the prognosis although 2 patients are alive five and eight years respectively after the onset of the disease the outlook for patients who have involvement of the bone is uniformly

poor. In 1 case involvement of the soft parts only was present. Treatment of multiple myeloma is doomed to failure from the beginning.

*Treatment of Osteogenic Sarcoma*—A study of 258 cases of osteogenic sarcoma treated by amputation selected from the first 400 cases in the Registry of Bone Sarcoma of the American College of Surgeons revealed that early amputation tends to hasten a fatal outcome.<sup>23</sup> Early amputation is interpreted as amputation within six months of the onset of symptoms. Survivors are defined as patients living with no evidence of tumor at the last report, more than five years after amputation and the last surgical treatment. Only 8 per cent survived early amputation whereas 29 per cent survived later amputation. In cases of sarcoma of a lesser degree of malignancy, 14 per cent of patients survived early amputation and 41 per cent survived delayed amputation. In cases of sarcoma of unusually high malignancy, 4 per cent of patients survived early amputation, and 37 per cent survived delayed amputation. When the cases of sarcoma of possibly low malignancy are excluded from among the cases of late amputation, 24 per cent of the patients in the remaining cases survived. This figure is three times as great as that for early amputation. The author feels that radiation is one means by which the development of recurrence after excision may be retarded. Also, he states that in the few cases in which bone grafts were inserted at the sites of excision of osteogenic sarcomas the development of recurrence was retarded. He believes that the bone graft occupies space which would otherwise be partly occupied by blood clot from which the fibrin might nourish or even stimulate fibroblastic cells. Also, the inserted bone stimulates the endothelial leukocytes which might retard the growth of the tumor cells. In conclusion, stress is laid on avoidance of early amputation and on irradiation before amputation or excision and implantation of a bone graft.

*Benign Chondromas of Ribs*—This is a review of the cases from the literature of benign chondromas of the ribs proved by biopsy or excision, together with 2 case reports.<sup>24</sup> There are various theories concerning the cause, the most probable being that the tumors arise from either cartilaginous fetal rests or islands of cartilage resulting from old rickets. Trauma seems to be significant in some of the reported cases. These tumors usually start insidiously and are of long duration. In regard to the pathologic picture, the benign central chondroma is a transition between osteochondroma and malignant chondromyxosarcoma. Adult cartilage predominates in its histologic picture. Changes may occur during development, so that the chondroma may become osseous chondroma or may undergo malignant degeneration to become a

23 Ferguson, A. F. J. Bone & Joint Surg. **22** 92, 1940.

24 Harper, F. R. J. Thoracic Surg. **9** 132, 1939.

chondromyxosarcoma The author states that there is a strong tendency for a high benign chondroma to undergo malignant degeneration Therefore, chondromas in the ribs are potentially malignant even though they may appear histologically benign Clinically a sudden increase in size of the tumor or an increase in the pain may indicate a turn toward malignancy Benign chondromas are very prone to recur, and incomplete removal seems to stimulate growth of the remaining tissue In 5 of 11 cases followed more than one year, the tumors recurred Treatment should consist of early and complete removal of the tumor It is often necessary to open or resect part of the pleura for complete removal Some authors advise radium or roentgen therapy after the operation

#### SHOULDER

*Traumatic Dislocation of the Tendon of the Biceps Brachii Muscle*—Abbott and Saunders<sup>25</sup> state that attritional changes play a part in dislocation of the tendon of the biceps brachii muscle but cannot ignore the definite and severe accidents associated with each of their cases They feel that forcible lateral rotation of the arm is the principal cause of dislocation The injury is followed by pain and swelling of the joint, with complete disability of the affected shoulder Weakness and limitation of motion in forward flexion and adduction of the shoulder are present, and forced supination of the forearm against resistance with the elbow held in flexion is painful The principal findings include swelling of the anterior aspect of the shoulder, tenderness (most pronounced over the bicipital groove) and a definite snapping sensation on abduction and external rotation of the shoulder In all of the 6 cases, which are reported in some detail, operation disclosed displacement of the tendon over the lesser tuberosity Fixation of the tendon in the bicipital groove is probably the quickest and best method of restoring function in a case of uncomplicated dislocation, but no rules as to the best procedure have been adopted Adequate results may be obtained by replacement of the tendon and repair by fascia of the roof of its groove

*Echinococcus Cyst of the Shoulder Joint*—Karageorgis<sup>26</sup> reports a case of echinococcus cyst of the shoulder joint capsule The patient was a 25 year old woman who for three years had suffered with articular pain and for two years with swelling The condition was diagnosed first as rheumatism, then as tuberculosis and finally as lipoma or foreign body reaction A posterior approach resulted in exposure of the cyst inside the joint capsule The cyst was filled with dead daughter cysts The postoperative course was uneventful, and the patient apparently recovered In Greece 1 other echinococcus cyst of the shoulder joint and 1 echinococcus cyst of the hip joint have been reported

<sup>25</sup> Abbott L C and Saunders J D de C M *Surgery* 6 817, 1940

<sup>26</sup> Karageorgis B *Zentralbl f Chir* 66 2006 1939

## KNEE

*Chondritis of the Knee* —Darrach<sup>27</sup> summarizes 376 arthrotomies of the knee for internal derangement. In 27.1 per cent of cases the anterior cruciate ligament was found to be partially or completely ruptured. In 51 per cent there was involvement of the articular cartilage. In 6.8 per cent of the cases in which it was present it was the only demonstrable lesion. Darrach stated: "In the majority of instances this condition involves only the superficial portion of the articular cartilage, and rarely does one see the underlying bone exposed." The term chondritis is suggested for this lesion, since osteochondritis applies only to conditions including involvement of bone. An incision large enough to enable one to explore the knee joint more thoroughly is advocated. The affected areas of cartilage are treated by shaving them off with a knife or a sharp gouge, leaving as smooth a surface as possible.

*Suppurative Arthritis of the Knee* —Maurer<sup>28</sup> reports 26 cases of suppurative arthritis of the knee joint treated in the Munich clinic in recent years. In all but 6 the condition followed direct injuries involving the joint (9 cases), the patella (7 cases), the femur (1 case) or the tibia (2 cases). In all cases a phlegmon of the capsule developed. Thirteen phlegmons were due to the streptococcus and 4 to the staphylococcus, 3 were due to a mixed infection. One was due to the pneumococcus. They were treated essentially by incision and drainage (anteriorly bilateral, and medioposterior incisions), followed by instillation of Chlumsky's phenol-camphor solution (phenol, 30 per cent, camphor, 60 per cent, alcohol, 10 per cent). Immobilization was stressed. Complications necessitated resection of condyles (5 cases), amputations (7 cases, with 3 deaths) and secondary closure (9 cases). In all, 4 patients (15.4 per cent) died of general infection. Blood transfusions were liberally resorted to. The end results in 26 cases were 3 joints with slight motion, 14 stiff joints, 4 thigh amputations, 4 patients dead and 1 unknown result.

[ED. NOTE. While a perfect result is rarely expected after suppurative arthritis of the knee joint, a better showing is usually made by those patients who are treated by adequate drainage and early motion.]

## FOOT

*Feet of Infants and Children* —Bloxsom<sup>29</sup> briefly reviews his records of footprints and heelprints showing the development of the longitudinal arch in 473 infants and children from 1 to 12 years of age. The rate

27 Darrach, W. *Ann Surg* **110** 948, 1939.

28 Maurer, G. *Arch f klin Chir* **197** 639, 1939.

29 Bloxsom, A. *Study of Feet of Infants and Children*, *Am J Dis Child* **59** 45 (Jan) 1940.

of development of the foot and its longitudinal arch varies considerably, but growth usually progresses most rapidly in children from 1 through 4 years of age. There are a certain number of children whose feet continue in a nondeveloping stage, and it has been found that corrective measures applied to these feet over years do no good. The author believes that the recording of footprints and heelprints of children is a valuable aid to the pediatrician.

#### INJURIES TO JOINTS

*Rarefaction of Bone After Injury to Joints*—Jaffe<sup>30</sup> reports 2 cases in which an acute trauma (without fracture) to a large joint resulted in severe rarefaction in the adjacent long bones. In 1 case the changes in the lower end of the femur were considered malignant, and the leg was amputated. In the other a biopsy specimen was taken from the lower end of the humerus, and the diagnosis of post-traumatic rarefaction was established. The roentgenogram shows round areas of rarefaction extending from just beneath the joint surface well into the medulla. The changes are probably due to a neurovascular derangement which with numerous dilated and engorged blood vessels results in localized bony rarefaction. Recovery is favored by active use of the part, with diathermy and massage.

*Painful Atrophy of Joints*—Ghormley<sup>31</sup> describes the clinical picture, diagnosis and treatment of post-traumatic painful atrophy of joints. The writer states that there may be considered to exist three types of atrophy: (1) Sudeck's "reflex" atrophy, (2) post-traumatic painful atrophy of joints, and (3) atrophy of disease. Post-traumatic painful atrophy of joints "may be regarded as a clinical entity perhaps as a variation of Sudeck's atrophy, although often its onset is slower than that of Sudeck's atrophy, and the symptoms are much less severe." One case is presented, in which arthrodesis of the knee was performed and led to a satisfactory outcome. This case offered material for study, which revealed marked bone atrophy, a dry joint and slight thickening of the synovial membrane, with a definite pannus-like membrane covering a portion of the surface of the joint. There was thinning of the articular cartilage and absence of all marrow elements. In addition to the known methods of treatment, administration of vitamin D and calcium is considered beneficial.

#### MISCELLANEOUS

*Gas Gangrene*—Williams and Hartzell<sup>32</sup> compare mortality statistics in cases of gas gangrene in San Francisco. In these cases the diagnosis

<sup>30</sup> Jaffe H. L. *Radiology* **33** 305 1939

<sup>31</sup> Ghormley R. K. *Arch Phys Therapy* **20** 725 1939

<sup>32</sup> Williams A. J. and Hartzell H. A. *West J Surg* **47** 59 1939

was proved clinically, bacteriologically and by roentgenograms. In the first series, treated from 1934 to 1937, the mortality rate was 58.3 per cent. In the second series, treated from 1936 to 1939, with benefit of roentgen therapy, the mortality rate was 8.3 per cent. In the series of 12 cases in which roentgen therapy was used, there were 4 patients who required amputation. Amputation was performed after roentgen therapy, and at the time of amputation no gas was noted in the soft tissues. Eight cases of arteriosclerotic gangrene complicated by gas gangrene are included. Four of the patients were treated with roentgen therapy, and 4 were not. All these patients died. Those that were treated with roentgen therapy showed no gas in the tissues at death. Of those who died after roentgen therapy 2 died of pulmonary embolism, 1 of pneumonia and 1 of arteriosclerotic heart disease. Two of the untreated patients died of gas gangrene.

#### FRACTURES AND DISLOCATIONS

*New Clavicular Splint*—A new type of clavicular splint applying the principle of suspension-elevation is used by Anderson<sup>33</sup> to treat fractures of the clavicle along correct anatomic and physiologic lines. At the same time it allows the patient to be up and about, wearing his usual clothing and retaining the use of both arms. The author states that convalescence is painless and that the splint is comfortable. Many patients return to work a few days after injury, and skilled and professional workers have continued to work regularly with the splint in place. The splint consists of (1) a body frame or base and (2) a rubber suspension axillary hammock. The advantage is saving of time and expense to both the patient and the physician.

*Injury of the Acromioclavicular and Sternoclavicular Joints*—Howard<sup>34</sup> reviews the salient features of anatomy, function and disability of the acromioclavicular and sternoclavicular joints and of fractures of the clavicle in the region of these joints. In treating severe sprains, subluxations and dislocations of the acromioclavicular joint he uses a modification of the Jones brachiooclavicular splint. To avoid pressure phenomena about the elbow, the elbow is immobilized in a well padded right angle posterior metal splint. The sling, running from the elbow to the clavicle, is taken care of by a slotted piece of felt. Pressure downward on the clavicle is made by a padded strap running over the clavicle and around the chest, near the opposite axilla. Dislocations of the sternoclavicular joint are treated by means of the clavicular cross. If the condition is adequately treated, operation is unnecessary in most cases.

33 Anderson, R. Surg., Gynec. & Obst. 69:770, 1939.

34 Howard, N. J. Am. J. Surg. 46:284, 1939.

*External Dislocation of the Elbow*—Griesemer<sup>35</sup> reports 6 cases of a rare condition, external lateral dislocation of the elbow. In 4 of these the condition was partial luxation, and in 1 it was a subepicondylar complete dislocation. The injury may result from a fall on the outstretched hand, a fall on the inner side of the elbow or a direct blow on the forearm. The outstanding physical finding is a widening of the transverse diameter of the elbow joint. Complications of this injury may be Colles' fracture, fractures about the elbow, capsular and muscular lacerations, Volkmann's ischemic paralysis and neural and vascular injury. Reduction is usually obtained by manipulation with the patient under anesthesia. The forearm is manipulated into strong pronation, at the same time it is extended, and lateral flexion and supination are continued. The elbow is immobilized in a posterior plaster splint in flexion and supination. Dislocations over eight to ten days old are rarely reduced without operation. The writer advocates early active mobilization within twenty-four hours in cases of closed reduction and in thirty-six hours in cases of open reduction. Within three or four weeks satisfactory function should be obtained in uncomplicated cases.

*Fractures of the Head of the Radius*—Discussing a group of 52 fractures of the head of the radius treated for the most part conservatively (only 3 were subjected to open operation), Burmann<sup>36</sup> comments on the necessity for initial immobilization for at least two weeks. Of the 24 patients treated by very early motion and physical therapy, 17 were left with functional disturbances of various degree. Of 28 treated by primary immobilization for two weeks before institution of motion, 7 were left with functional disturbance. In general, the end results for all incomplete fractures and for complete fractures without dislocation were good. The results of the few complete or partial resections of the head of the radius were not satisfactory.

*Isolated Fracture of the Capitulum and Trochlea Humeri*—Czembirck,<sup>37</sup> reporting 2 cases in which this fracture followed a fall on the extended arm, points out that the mechanism described by Bohler for this fracture, namely, a fall on the bent elbow with the arm in abduction, is not the only mechanism involved. In an 18 year old patient seen soon after injury, he removed the fragment. The result was a 30 degree limitation in flexion and a 30 to 40 degree limitation of extension. In a 15 year old patient he replaced the fragment. The result was full flexion with 40 degrees of limitation of extension.

*Fracture of the Carpal Navicular Bone*—Cave<sup>38</sup> stresses the importance of early diagnosis and adequate early treatment of injuries to the

35 Griesemer, W. D. *Am J Surg* **47** 57 1940

36 Burmann, C. *Arch f klin Chir* **197** 115 1939

37 Czembirck, L. *Zentralbl f Chir* **66** 1086 1939

38 Cave, C. F. *The Carpus with Reference to the Fractured Navicular Bone* *Arch Surg* **40** 54 (Jan) 1940

navicular bones. He believes that practically all navicular fractures heal if recognized and treated by early prolonged immobilization in plaster with the wrist in dorsal flexion and radial deviation. For nonunion the introduction of an autogenous bone graft through a drill hole in the bone, followed by prolonged fixation in plaster, seems to produce the most satisfactory results.

*Slipped Femoral Epiphysis*—Ghormley and Fairchild<sup>39</sup> report the results of treatment of 55 patients with slipped upper femoral epiphysis. Twenty-six gave a definite history of severe injury to the hip. In 21 there was a gradual onset of symptoms. Males outnumbered females more than 3 to 1. Sixty-one per cent were normal or slightly above normal in weight. The age varied from 9 to 18, with the majority between 13 and 16 years. Some were adults with old deformities. Three patients were treated with a cast alone. Of these, 1 had a good result and 1 a fair result, the other was unchanged. Eight were treated by manipulation, with good results for 6, a fair result for 1 and a poor result for 1. Open reductions were done in 6 cases, with good results in 2, a fair result in 2, a poor result in 1 and an unknown result in 1. No internal fixation was used in 4 cases, and a bone screw was used in 1. Osteotomy of the femoral neck was done in 11 cases, in 7 without internal fixation, in 3 with beef bone screws and 1 with Kirschner wires. Of the patients in this group, 6 had good results, 3 had fair results, in the case of 1 it was too early to judge, and 1 was lost. In 12 cases of a preslipped stage of the disease, conservative treatment (splints, braces, crutches, physical therapy) was used. In 8 of these there were good results, in 2, fair results, in 1, poor results, and in 1, unknown results. The authors feel that early diagnosis and protection against further slipping by conservative measures can preserve a fairly normal hip. Closed reductions can be done only early and by the gentlest manipulation. In open operations when the epiphysis is not free they believe that a cuneiform osteotomy through the neck can be done with least damage to the epiphysis.

*Fracture of the Femoral Neck Due to Metrazol Therapy*—Schizophrenic patients treated with metrazol have very severe muscular spasmodic contractions, which have been responsible for 23 fractures reported in the literature. (Eight were of the femoral neck, 2 bilateral.) Struppler<sup>40</sup> adds 2 more cases in which epileptiform convulsions of great severity resulted in fractures of the femoral neck requiring metallic fixation. He suggests that the patients be supported in bed with the hips and knees flexed during administration of the drug. He hopes that

39 Ghormley, R. K., and Fairchild, E. D. Diagnosis and Treatment of Slipped Epiphyses, *J. A. M. A.* **114** 229 (Jan. 20) 1940.

40 Struppler, C. *Arch. f. klin. Chir.* **197** 628, 1939.



this position of joint relaxations may minimize the effect of muscle contractions. Clinically, it apparently has made the cramps much easier to bear.

*Ununited Fractures of the Femoral Neck in the Aged*—Gallie and Lewis<sup>41</sup> present their experience in the treatment of fractures of the femoral neck in the aged, based on 15 cases of use of a Smith-Petersen nail together with a bone graft. The technic consists of placing a nail close to the lower border of the neck, drilling a  $\frac{1}{2}$  inch (1.2 cm) hole parallel to the nail in the upper portion of the neck and inserting a bone graft from the fibula or a suitable piece of bone from the crest of the ilium or the tibia. Union took place more slowly than in fresh fractures, but most of the patients were up in a chair in six months and walking after two or three months more.

*Staple for Transverse Fractures of Long Bones*—Lexer and Large introduced a U-shaped nail, really a staple with an elongated central portion. Both limbs of the staple were sharpened for introduction into the shaft of the bone so as to bridge the break. Andreesen<sup>42</sup> has modified this staple and in addition fastens it to the bone by circular wire encompassing the bone above and below the fracture. It replaces a "Lane plate." The modified nail is three sided, has its ends shortened to 0.4 to 0.5 cm and is notched in various places on its external surface to insure that the circular ties will stay in place.

*Fractures of the Tibial Plateau*—Fractures of the tables of the tibia constitute about 3 per cent of fractures of the leg and may occur at any age after adolescence. Fractures of one table are more common than fractures of both tables, and 70 per cent involve the external table. The cause is usually indirect, the femoral condyle coming down on the tibial plateau with the knee in a valgus position. Central compressions probably result from the menisci taking the blow from the outer rim. Gerard-Marchant<sup>43</sup> divides these fractures into two types, separation fractures and compression fractures. A separation fracture is one in which the fractured table is separated from the main portion of the tibia, but without impaction. There are several types of separation fracture, depending on the point at which the fracture line enters the articular surface. The fragment may be displaced in any direction and is sometimes rotated. The compression type of fracture may consist of a central or a marginal depression or the entire tuberosity may be impacted. A third type of fracture is a combination of the separation and compression fracture. There may be associated lesions such as fractures of the tibia

41 Gallie W. F. and Lewis F. I. *J. Bone & Joint Surg.* **22**: 76, 1940.

42 Andreesen R. *Zentralbl. f. Chir.* **66**: 1552, 1939.

43 Gerard-Marchant P. *Rev. d'orthop.* **26**: 499, 1959.

tubercle, the tibial spine or the fibula. Ligamentous lesions usually involve the opposite lateral ligament. Cartilaginous injuries are frequent and are a major problem. Treatment consists of either closed or open reduction. There are several methods of closed reduction in common use. Manual reduction consisting of strong traction followed by adduction or abduction, combined with moldings, is often an efficient method. This will not be of any use in a centrally depressed fracture. Instrumental reduction is frequently utilized and may consist of traction by a Kirschner wire or the use of compressing instruments, mallets or Bohler's method of prying up the fragment by insertion of a nail. The last-mentioned method was not satisfactory in the author's hands. Fixation after closed reduction is usually by plaster, although some prefer continuous traction. For the latter method to be efficacious, the fragment under traction must be higher than the other, and the other fragment must be fixed by capsular or ligamentous attachment. Traction is of definite value in fractures of both tuberosities.

Open operation may be done either with or without opening of the knee joint. There are a great many incisions in use, but the surgeon should strive to get good exposure, particularly of the lower and posterior part of the fragment, in order to facilitate the repair. By doing an arthrotomy at the time of operation, the surgeon has the advantage of better visualization of the fragments and also the ability to inspect the meniscus. The latter is undoubtedly torn in many cases, and the diagnosis cannot be made without opening the joint. The opponents of arthrotomy raise the objection that opening the knee has special risks, and that it may be followed later by arthritis. In general, arthrotomy should be done if the fracture is complex, if the meniscus is suspected of being torn or if there is a tibial fragment in the joint.

Reduction of the fragments is often difficult even with wide exposure. The fragments may be solidly impacted and crushed together. The act of prying up the fragment may easily crush the spongy bone and create a large defect interior to the raised fragment. The perfection of reduction should be judged by reestablishment of the articular surface. After reduction the fragments are never stable enough to leave without internal fixation. Various forms of internal fixation are in use. Nails do not hold well in the soft bone. If screws are used, they should be long and relatively thick. Two screws are better than one, and the fragment should be temporarily fixed with wires to prevent displacement while the screw is being inserted. Bone grafts may also be used for fixation. Grafts do not give as firm fixation as does metal, and they are useless for the separation fracture. Bone grafts have their greatest usefulness in the impacted fractures, in order partly to fill the defect remaining after reduction.

ORTHOPEDIC OPERATIONS

*Reconstructive Operations for Septic Arthritis of the Hip Joint*—Hallock <sup>44</sup> presents end result studies on 38 patients who had 46 operations for reconstruction or stabilization of a hip joint that had been damaged or destroyed by previous suppurative arthritis. There were 20 reconstructions, 4 arthroplasties, 7 shelf stabilizations and 15 fusions. The results indicate that reconstructive procedures in children generally control dislocation and eliminate pain but leave considerable limitation of motion. Pain is likely to develop in adult life because of poor mechanics. Arthroplasties may prevent late development of pain, but many patients do not have enough residual bone for this type of procedure. Well constructed and well placed shelves, unless absorption ensues, will provide dislocated hips with stability and fairly good ranges of motion. Fusions, however, can be relied on to provide stable hips free from pain and without marked limp unless poor position is obtained or there is too much shortening. Early diagnosis and drainage of septic hips will decrease the necessity for reconstruction operations. If operations are to be done, it is advisable to wait two to three or more years after cessation of all drainage or other evidence of activity.

*Excision of the Patella for Arthritis of the Knee Joint*—Berkheiser <sup>45</sup> discusses the morphology and comparative anatomy of the patella and the role of the patella in the mechanism of the knee joint. He then presents a series of 11 cases in which the patella was excised for arthritis of the knee, the aim being to relieve the patient of pain on extension and to increase the range of motion. The operation and the postoperative care are described, and 2 cases are given in some detail. The results of this operation were satisfactory in 8 cases and only fair in 3, which were not well selected. In general there was relief of pain and increase in function.

*Lengthening of the Tibia and Fibula*—Abbott and Saunders <sup>46</sup> report on the further development of lengthening of the tibia and fibula. There are certain patients in whom epiphysial arrest is no longer applicable, because they have reached maturity. There are others, of short stature, in whom further reduction in height is undesirable especially patients with marked degree of shortening, furthermore, it is to be borne in mind that shortening of the leg is carried out on the sound limb and on this ground may be objected to by the patient. Such indications,

<sup>44</sup> Hallock, H. Reconstructive and Stabilizing Surgery for Residual Suppurative Arthritis of Hip Joint. Study of Forty-Six Unselected Cases, J. A. M. A. **113** 2398 (Dec 30) 1939.

<sup>45</sup> Berkheiser, E. J. Excision of Patella in Arthritis of Knee Joint. I. A. M. A. **113** 2303 (Dec 23) 1939.

<sup>46</sup> Abbott, I. C. and Saunders, J. B. de C. M. Ann Surg. **110** 961, 1939.

the authors feel, make it desirable to retain the procedure of leg lengthening for a limited group and prompted them to do further studies with a view to reducing the chances of complications. Among the complications were deformities of the knee and of the ankle, malunion or nonunion, limitation of joint motion, muscle weakness, neural and circulatory disturbances, infection, and aseptic necrosis. To overcome these difficulties they describe an operation based on new principles. These involve complete division of the deep fasciae of the leg, the intermuscular septums and the interosseous membrane, as well as freeing of all the important blood vessels and nerves at the upper portion of the leg. Special osteotomies have been devised to retain the maximum portion of the origin of the muscles. A new apparatus has been used, which, they believe, gives better control of the fragments and offers less chance of infection of the pin wounds. They emphasize that the operation of leg lengthening is and in all probability always will be a major undertaking, with the possibility of serious complications. The procedure demands an intimate knowledge of anatomy and a careful study of every stage of the operation and postoperative care. The report covers 7 cases of treatment by the new method.

*Fusion of the Ankle*—King<sup>47</sup> reports the results of ankle fusion in 106 patients operated on at the New York Orthopedic Dispensary and Hospital from 1934 to 1938 inclusive. In 72 patients ankle fusion was performed for paralytic drop foot. In 66 of these patients a subtalar triple arthrodesis had been carried out previously for lateral instability of the foot. In 19 of 23 patients with drop foot and unstable knee the knee was stabilized by ankle fusion. Ankle fusion was performed in 34 cases for paralytic calcaneus deformities. In 9 of these the patients also had an unstable knee, in 8 the knee was stabilized by ankle fusion. In 85 cases, or 80 per cent, the end result was considered good. In 10 cases, or 9 per cent, it was only fair. In no case was the result considered poor. The author recommends fusion in 5 to 10 degrees of equinus for males and 10 to 15 degrees of equinus for females.

*Correction of Congenital Subluxation of the Fifth Toe*—Congenital varus deformity of the fifth toe with subluxation of the fifth metatarsophalangeal joint appeared in 60 cases during the past five years at the New York Orthopedic Dispensary and Hospital. Lantzounis<sup>48</sup> has performed 25 operations to correct this condition. Excellent results were obtained in 16, good results in 4 and poor results in 3. One patient was not seen after operation. One patient in the group in which the results were poor was operated on at the age of 2 years, which the author

<sup>47</sup> King, B. B. Ankle Fusion for Correction of Paralytic Drop Foot and Calcaneus Deformities, *Arch Surg* 40:90 (Jan) 1940.

<sup>48</sup> Lantzounis, L. A. *J Bone & Joint Surg* 22:147, 1940.

feels is too young. The operative technic consists of making a 2 inch (5 cm) longitudinal incision over the dorsal aspect of the fifth metatarsophalangeal joint. The extensor digitorum longus tendon of the fifth toe is isolated and divided at the distal end of the incision. The periosteum of the distal end of the fifth metatarsal bone, the capsule and the periosteum of the proximal phalanx are incised longitudinally and are then elevated subperiosteally from the dorsal, lateral and medial surfaces, their plantar attachment being left undisturbed. A drill hole is made in the distal end of the fifth metatarsal bone, and the proximal portion of the previously severed tendon of the extensor digitorum longus muscle is threaded through and sutured back onto itself. A mattress suture is placed in the periosteocapsular flap, the toe is then plantar flexed, and the mattress suture is tied. As a result of the tension exerted by the periosteocapsular flap, the toe is then stable, occupying a normal position without support.

#### RESEARCH

*Phosphatase Activity in Early Callus*—Tollman and his associates<sup>49</sup> studied the relation of blood phosphatase, tissue phosphatase, tissue calcium and tissue metabolism in a series of rabbits subjected to osteotomy of the radius. They found no definite relation between the level of blood phosphatase and the healing of fractures. There was an irregular increase in tissue phosphatase activity and calcium deposition with time. A close relation was found between the phosphatase activity of the callus and the amount of calcium deposition. There was an initial rise in tissue metabolism of the callus, followed by a fall.

*Bone-Regenerating Activity of Periosteum*—Levander<sup>50</sup> attempted to find by animal experimentation what ability to form bone there was in the periosteum. In adult animals periosteum was removed and transplanted under the skin. In none of the 9 animals used was there any bone regeneration. In young animals, similar subcutaneous transplantations showed new bone formation in 33 per cent for homotransplantation in 6 animals and in 25 per cent for autotransplantation in 8 animals. The new bone develops out of newly formed mesenchymal tissue at the seat of implantation. Implantation of bone, periosteum and bone marrow in 11 animals subcutaneously led to the production of bone. Of 5 animals with autotransplantation 2 showed bone regeneration. The author believes that some substance is liberated from living bone tissue which possesses the power of activating nonspecific mesenchymal tissue and causing it to become differentiated into cartilaginous or bony tissue. The cellular

49 Tollman J P, Drummond D H, McIntyre A R and Biskard J D. Tissue Metabolism and Phosphatase Activity in Early Callus. Arch Surg 40:43, (Jan.) 1940.

50 Levander G. Acta chir Scandinav 83:1 1939.

mesenchymal layer of the periosteum should be regarded as part of the bony tissue itself. Periosteum should be reserved as the term for the connective tissue membrane which at all ages surrounds all bony tissue.

*Joint Cartilage Under Various Physiologic Demands*—Freund<sup>51</sup> presents a study of the response of cartilage to certain functional stimuli. The behavior of cartilage under ultraphysiologic conditions (increased pressure) and infraphysiologic conditions (disuse) is discussed. Both of these factors, a disuse and overuse, are analyzed in the case of an 18 year old patient with spastic quadriplegia and athetosis. Thorough macroscopic and microscopic studies of joint surfaces are made and compared with normal. Freund concludes that functional stimuli below or above the physiologic optimum, if active over a long period, are deleterious to joint cartilage. The damage does not remain limited to the joint cartilage in growing persons but draws the bony portion of the epiphysis into participation by stopping further enchondral ossification. Whether the pressure force is intense and working over a relatively short period or whether it is still within physiologic limits but of protracted or even continuous action, the result will be the same. The joint cartilage will lose its normal elasticity and will suffer irreparable damage. Any marked alteration of function for a long period is certain to lead to degenerative changes of joint cartilage and may be followed by the whole syndrome of fully developed arthritis deformans.

*Transplanted Epiphysial Cartilage*—In an effort to lengthen bone, Bisgard<sup>52</sup> transplanted full segment thicknesses of epiphysial cartilage from the femur into the tibia, which had been divided transversely. The segments consisted of epiphysial cartilage plate with adjacent bone and constituted less than half of the plate. Eight goats approximately 1 month old were used. One animal lost its leg as a result of circulatory interference, and 1 had an infected wound with loss of the graft. In the remaining 6 goats union occurred. The animals were observed for three months. All growth took place at the epiphysial ends. In no instance was length gained at the site of bisection. In fact, there was preliminary shortening from absorption either of bone at the severed ends of the tibia or of cartilage of the graft.

*Lymph Spaces of Normal and Diseased Meniscus*—Fifty-three studies of the vascular supply of the menisci indicate they are avascular save for the anterior and posterior ends of their attachment. They rely on the lymphatics for resorption and are provided with long broomlike strands of lymphatics, which follow the course of the fibers.

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51 Freund, E. Joint Cartilage Under Infraphysiologic, Ultraphysiologic and Euphyiologic Demands, Arch Surg 39 596 (Oct) 1939

52 Bisgard, J. D. Transplanted Epiphysial Cartilage, Arch Surg 39 1023 (Dec) 1939

that make up the meniscus. They are demonstrated by the hydrogen peroxide method of Mangus, in which bubbles of gas liberated by the decomposing chemical as part of a catalytic reaction to tissue fluids fill the lymph channels and permit them to be studied. Rostock<sup>53</sup> reproduces studies of normal and abnormal lymph channels in degenerated and regenerating menisci. In a regenerated meniscus, apparently the lymph channels begin in time to approach the normal pattern as the tissues of the new meniscus respond to the demands of function.

[ED NOTE. This is an interesting study. Too sweeping conclusions cannot be drawn from studies with hydrogen peroxide alone. Tissue spaces and blood vessels can be spread out by the catalytic action, and these can be confused with lymphatics.]

*Pathologic Picture of Malacia of the Lunate Bone*—Nagura<sup>54</sup> working in Japan presents an interpretation of the zones of repair in cases of malacia of the lunate bone. In his opinion, he has found the key to the pathogenesis. He finds the areas similar to those associated with other aseptic necroses of bones. As the result of an injury, the articular cartilage and the spongiosa are broken, and a fissure extends into the spongiosa. Instead of the spongiosa healing with bone, chondroblasts from the cartilage-spongiosa boundary invade the cleft resulting from the trauma and go on to form a cartilage plane segregating the fracture area. This plane grows in thickness, and the fractured-off area protrudes into the joint space, where it is subjected consequently to further trauma. The bone is weakened, and the remaining bone breaks down under trauma. The areas of cartilage repair degenerate, and a giant cell, foreign body reaction type of repair follows, which marks the site of necrotization. Only the volar half of the bone remains. Pathologic sections are reproduced in support of his explanation of the course of events.

*Effects on Ribs of Increased Intramedullary Pressure*—Using a modification of a method described by Larsen in 1938, Cressman and Blalock<sup>55</sup> present work which was carried out on the ribs of dogs. The experiments demonstrate that the cortex and the marrow may be killed and the periosteum separated by increased intramedullary pressure. In the absence of infection, periosteum is reattached and new bone is laid down, substituting the necrotic bone with sequestration. Non-toxin-producing organisms are well tolerated and result in hardly more alteration of the rib than does pressure alone. Toxin-producing staphylococci cause necrosis of bone and marrow and when combined with the necrosis succeeding on elevated intramedullary pressure cause extensive necrosis.

53 Rostock P. Arch f klin Chir. **197** 782 1940

54 Nagura S. Arch f klin Chir. **197** 405 1939

55 Cressman R. D. and Blalock A. Surgery **6** 535 1940

and sequestration which greatly resemble osteomyelitis in the human being. Necrosis of bone produced by elevated intramedullary pressure and the presence of virulent organisms, whether implanted directly or localized from the blood stream, leads to sequestration. The sequestrums, however, need not be extruded, as they are absorbed in situ.

*Experimental Arthritis in Rabbits*—Cecil and his co-workers<sup>56</sup> report that they produced arthritis in rabbits with hemolytic streptococci and *Streptococcus viridans* introduced intravenously. They were able to produce arthritis by intravenous injection of *Staphylococcus aureus*, *Bacillus paratyphosus* A and *Pneumococcus*, but not with a number of other organisms which were tried. When streptococci were introduced into other sites, particularly the gums and sinuses, the animals had arthritis, depending on the degree of invasion of the blood stream and not from late dissemination of bacteria from an infected focus. Arthritis usually developed during the stage of bacteremia. Streptococci were repeatedly grown from the synovial fluid during the first two or three weeks after injection but seldom thereafter. The sedimentation rate was increased and the agglutinin titer elevated in a very high percentage of cases in which streptococci were injected. The pathologic changes taking place in the joint are described and are similar to the changes associated with rheumatoid arthritis in man. Although staphylococci produce marked suppuration in the joints, there was little difference in the pathologic picture after subsidence of the acute infection from that of arthritis produced with streptococci.

*Notch Shadows in Lateral Roentgenograms*—In an anatomic study of the vertebral bodies of fetuses and newborn infants, Wagoner and Pendergrass<sup>57</sup> described the "notch" seen in lateral roentgenograms of the vertebral bodies. They found that the posterior "notch" shadow results from the presence of an actual indentation in the posterior wall of the body and is the point of entrance of the posterior arteries or veins. The anterior "notch" results from the presence of a large sinusoid space within the vertebra.

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<sup>56</sup> Cecil, R. L., Angevine, D. M., and Rothbard, S. *Am J M Sc* **198** 463, 1939.

<sup>57</sup> Wagoner, G., and Pendergrass, E. *Am J Roentgenol* **42** 663, 1939.



## EXPERIMENTAL STUDIES ON HEADACHE

### PAIN-SENSITIVE STRUCTURES OF THE HEAD AND THEIR SIGNIFICANCE IN HEADACHE

BRONSON S RAY, M D

AND

HAROLD G WOLFF, M D

NEW YORK

Studies on man and lower animals have shown that the cranial blood vessels are pain-sensitive structures, capable under special circumstances of giving rise to headache<sup>1</sup> The distention of cerebral arteries is primarily responsible for the headache produced by certain chemical agents, of which histamine is representative,<sup>2</sup> the headache associated with septicemia and fever is in the same category<sup>3</sup> It has been shown that the afferent fibers from the pain-sensitive cerebral arteries above the tentorium enter the brain stem primarily through the fifth cranial nerve, whereas the fibers from the arteries below the tentorium enter the nervous system chiefly through the upper cervical nerves<sup>4</sup> The disten-

From the Departments of Surgery and Medicine of the New York Hospital and Cornell University Medical College

1 (a) Leake, J P, Loevenhart, A S, and Muehlberger, C W Dilatation of Cerebral Blood Vessels as a Factor in Headache, *J A M A* **88** 1076 (April 2) 1927 (b) Hitz, J B, and Kammer, A G The Effects of Stimulation of Cerebral Blood Vessels, Thesis, University of Wisconsin Graduate School, 1926, cited by Leake, Loevenhart and Muehlberger (c) Levine, M, and Wolff, H G Afferent Impulses from the Blood Vessels of the Pia, *Arch Neurol & Psychiat* **28** 140 (July) 1932 (d) Wolff, H G Headache and Cranial Arteries, *Tr A Am Physicians* **53** 193, 1938

2 (a) Pickering, G W and Hess, W Observations on the Mechanisms of Headache Produced by Histamine, *Clin Sc* **1** 77, 1933 (b) Clark, D, Hough, H B, and Wolff, H G Experimental Studies on Headache Observations on Histamine Headache, *A Research Nerv & Ment Dis, Proc* (1934) **15** 417, 1935 Experimental Studies on Headache Observations on Headache Produced by Histamine, *Arch Neurol & Psychiat* **35** 1054 (May) 1936

3 (a) Sutherland A M, and Wolff H G Experimental Studies on Headache Observations on Mechanism of Headache in Migraine, Hypertension and Fever Therapy, *Tr Am Neurol A* **64** 103, 1938 (b) Pickering G W Experimental Observations on Headache, *Brit M J* **1** 907, 1939

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tion of certain branches of the external carotid arteries is chiefly responsible for migraine headache and the headache associated with arterial hypertension <sup>5</sup>

Thus, data about the great variety of headaches resulting from distention of cranial arteries are specific, but there is lacking detailed information about the sensitivity to pain of the majority of the structures of the head, essential to an understanding of other varieties of headache. Moreover, little precise information exists concerning either the sites of reference when pain-sensitive structures are stimulated or of the pathways that convey the impulses interpreted as headache. The demonstration at postmortem examination and by histologic methods of the presence of nerve fibers or nerve endings in a given structure does not in itself justify the inference that the structure is sensitive to pain, afferent fibers cannot be distinguished with certainty from efferent, nor can pain-conducting afferent fibers and end organs be differentiated from other afferent nerves. It is desirable, therefore, to turn to a more direct method of study, and to this end an excellent opportunity is offered during surgical procedures on the head.

Surgeons who employ local anesthesia during surgical procedures on the brain are aware that some intracranial structures are more sensitive than others. However, impressions with regard to sensitivity may be inexact unless special care is taken to make accurate and repeated determinations and recordings. Valuable observations concerning sensitivity to pain have already been made <sup>6</sup>

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<sup>5</sup> Graham, J. R., and Wolff, H. G. Mechanism of Migraine Headache and Action of Ergotamine Tartrate, *A. Research Nerv. & Ment. Dis., Proc.* (1937) **18** 638, 1938, *Arch. Neurol. & Psychiat.* **39** 737 (April) 1938. Sutherland and Wolff <sup>12a</sup>

During the last five years an attempt has been made in this clinic to acquire in an orderly way from patients during operative procedures a more exact knowledge of the sensitivity to pain of structures inside and outside the cranium. It is the purpose of this communication to present the data thus acquired and to consider their clinical significance.

#### METHOD

As a basis for this study, there was selected from a large group a limited series of 30 patients.<sup>7</sup> The following conditions were required:

- 1 Surgical exposure of the lesions of the brain afforded an opportunity to make careful observations on the sensitivity to pain of the structures within and outside the cranium.

- 2 The patients were intelligent and cooperative, so that not only could pain be reported but its site and nature could be described.

- 3 The patients were relatively free of apprehension and of preoccupation with pain, so that a minimal amount of local and general analgesia was required.

- 4 The operative procedures were such that the patients were not too prostrated or inarticulate to describe their sensations.

- 5 The structures in every case were free of any disease process. This was necessary to insure normal responses to stimulation.

- 6 The observations were recorded in detail and by appropriate charts at the time they were being made in the operating room. The records included the site and kind of stimulation and the localization and nature of the pain when it resulted.

The type of stimulation employed in each instance will be included in the data on the following structures:

#### OBSERVATIONS

*Scalp, Galea, Fascia and Muscle*—One hundred and fifty observations were made on 30 subjects.

The scalp was sensitive to all the usual forms of thermal, chemical, mechanical and electrical stimulation. The galea was sensitive to pain but otherwise insensitive. Where the blood vessels were in close contact

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New Points in Its Anatomy, Physiology and Pathology, *J Neuropath & Psychopath* **17** 193, 1937. (l) Northfield, D W C. Some Observations on Headache (Hunterian Lecture Abridged), *Brain* **61** 133, 1938. (m) Penfield, W, and McNaughton, F. Dural Headache and the Innervation of the Dura Mater, *Tr Am Neurol A* **64** 106, 1938. (n) McNaughton, F. The Innervation of the Intracranial Blood Vessels and Dural Sinuses. *A Research Nerv & Ment Dis, Proc* (1937) **18** 178, 1938. (o) Fay, T. Problems of Pain Reference to the Extremities, *Am J Surg* **44** 52, 1939.

7 Observations on 15 additional cases have verified the foregoing data.

with the galea there was usually greater sensitivity to pain than at other places. The fascia covering the temporal and occipital muscles and also the muscles themselves were everywhere sensitive to pain. The pain arising in all these structures usually was experienced somewhere near the region of the stimulus.

*Periosteum of the Skull (Epicranium)*—One hundred observations were made on 30 subjects.

The periosteum had a variable sensitivity to pain. On the whole it was not particularly sensitive, and in spots over the vertex it was entirely insensitive. In general, the sensitivity increased in the regions just over the brow, low in the temporal regions and low in the occipital regions. Always when a periosteal elevator was used to strip up the periosteum around the base of the skull there was a complaint of moderate pain, felt somewhere in the neighborhood of the point of stimulation.

*Cranial Bone, Including Diploic and Emissary Veins*—The cranial bone was everywhere insensitive. This was demonstrated many times in the process of drilling, sawing, rongeur-ing and coagulating at all points of the skull. This general statement is valid for the inner and outer tables and the cancellous central portion. It may further be stated that when there was occasion to test for pain in regions of endostoses and exostoses, which were sometimes highly vascularized, there was still no evidence of sensation (3 subjects, 12 observations). The venous channels (diploic veins) of the bone were also insensitive on faradic stimulation (3 subjects, 12 observations). There was occasion to stimulate directly the walls of some of the larger diploic veins both with faradic current and by the coagulating endothermy, no pain was elicited. Specifically, the principal diploic veins studied were the occipital, the mastoid and the large lateral venous channels. The walls of the occipital and mastoid emissary veins just outside the skull (fig 1 A) were directly stimulated with faradic current and found to be insensitive (3 subjects, 12 observations [fig 1 A]).

*Extracranial Arteries and Veins*—All of the arteries of the scalp were found to be sensitive to pain, whereas the veins were much less so or not at all (fig 1 B). The principal extracranial artery is the superficial temporal, which is a branch of the external carotid artery and supplies the larger portion of the parietal region. The supraorbital and the frontal arteries are branches of the ophthalmic artery (itself a branch of the internal carotid artery) and supply the frontal region. The occipital arteries and the postauricular arteries are branches of the external carotid artery and supply the occipital and suboccipital regions. There are veins corresponding to each of these main arteries. By various methods it was demonstrated that the main trunks of all of these arteries

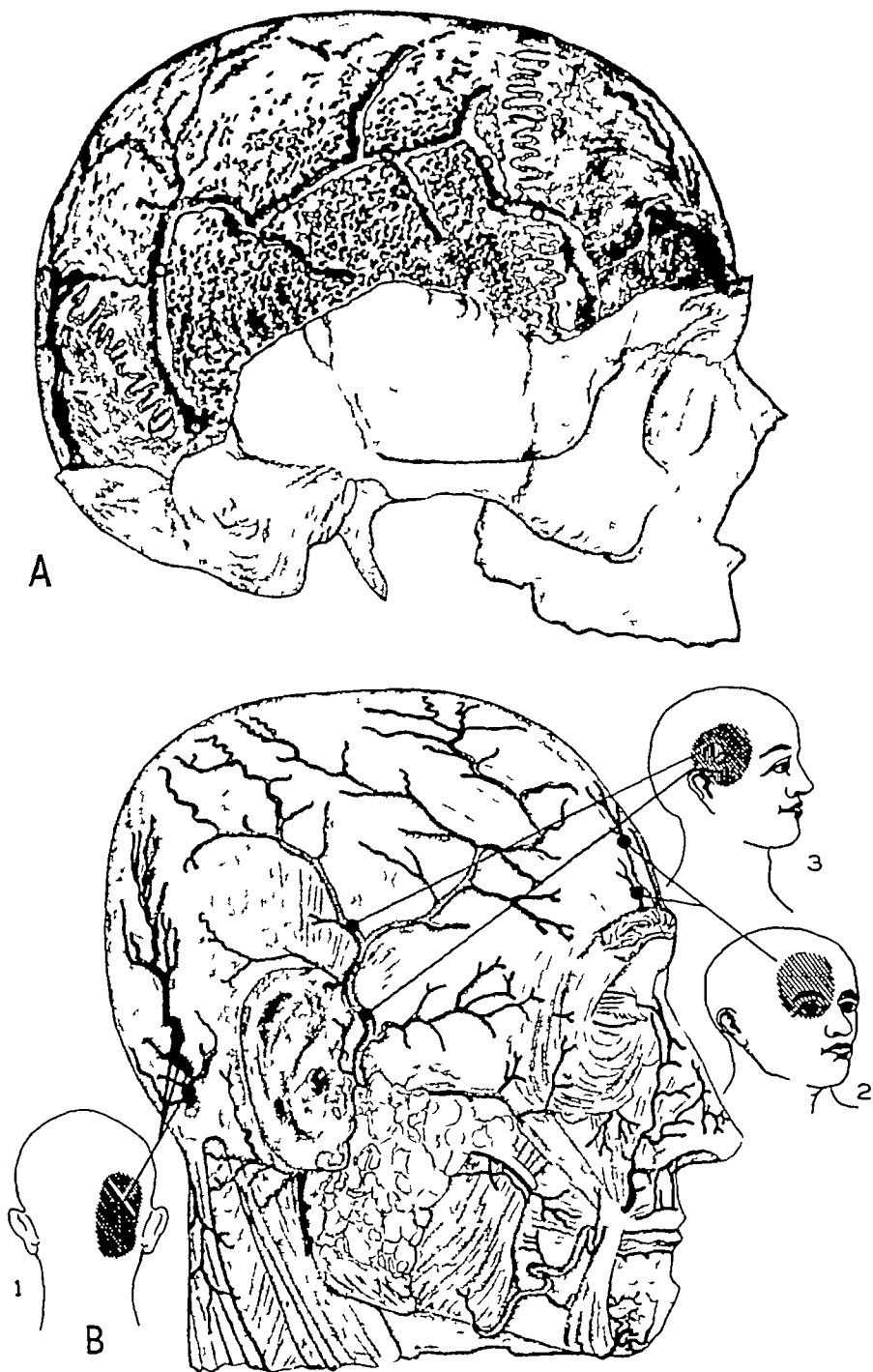


Fig 1—*A*, view of the diploic and emissary veins of the cranium ○ indicates the point of stimulation without pain *B* view of the arteries of the scalp ● indicates the point of stimulation causing pain The diagrams show the area of pain following stimulation of (1) the occipital arteries, (2) the supraorbital and frontal arteries, and (3) the superficial temporal artery

were sensitive to pain. The stimuli employed included faradic current, burning, distending, stretching and crushing (temporal artery, 6 subjects, with 24 observations, occipital artery, 5 subjects, with 20 observations, frontal and supraorbital arteries, 2 subjects, with 8 observations)

Stimulation of two different points 3 cm or more apart caused pain which was localized at slightly different sites. Charts of the observations showed that in each instance the pain was felt in the general region of the point of stimulation and that stimulation of both points at once produced pain over a larger area than a combination of the two painful areas produced previously (fig 2)

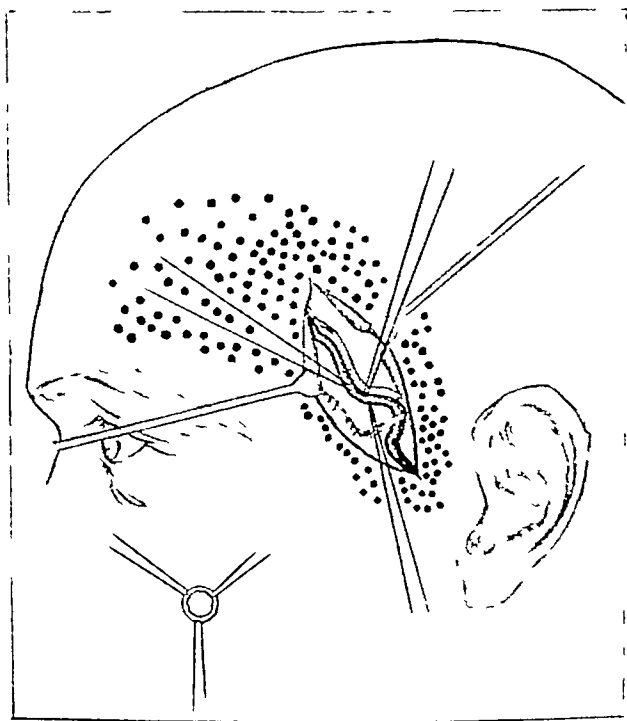


Fig 2—View of traction sutures symmetrically placed in the wall of the superficial temporal artery. The mechanical distention of the artery resulting from simultaneous traction on all three sutures caused pain in the dotted area.

Distention of an artery by stretching its walls with the spread of a clamp inside its lumen elicited pain, and an intermittent pain followed alternate spreading and closing of the clamp. Distention was effected in still another way, by means of three fine silk threads attached to the wall of the temporal artery and so spaced in relation to each other that when they were pulled simultaneously the temporal artery was distended without interference with the blood flow. Passing the fine curved needles through the outer layers of the arterial wall produced no sensation. Gentle pressure likewise was not perceived, although pinching was associated with pain. It was observed that distention induced in the manner indicated, that is, by pulling the three threads simultaneously, produced a

well localized pain in the temporal region, in an area about 5 cm in diameter. The pain was aching, persisted as long as distention was maintained and promptly ceased when it was discontinued. By repeatedly and rhythmically distending and collapsing the artery a throbbing quality could be given to the headache. When the threads were applied in the aforementioned manner in two places, one nearer the ear and one about 1.5 cm farther toward the temporal region, distention by pulling on either group of threads produced pain similar to that just described, but the areas of discomfort were separately located, the one nearer the ear and the other over the temple. When the two groups were pulled simultaneously, so that distention occurred at two separate sites, the ache seemed to be more widespread than the sum of the two painful areas produced previously, and the headache then seemed to reach from the front of the ear to the middle of the supraorbital ridge. The headache resulting from this distention was associated with a feeling of nausea or sickness. Longitudinal stretch of an artery was painful in the same manner as the lateral stretch of distention.

Constriction of the lumen was not painful. The repeated application of epinephrine to exposed and otherwise pain-sensitive arteries caused vigorous constriction of the vessels but no pain. Crushing and stroking of the arterial wall always resulted in pain.

In all such experiments no procaine hydrochloride was employed in the region about the artery. The introduction of procaine hydrochloride into the adventitia of the temporal artery immediately produced anesthesia to all stimuli a few centimeters distal to the point of injection. The implication is that the sensory nerve supply originates near and travels along with the arteries. It should be pointed out that sometimes a number of small visible nerves were seen passing along the course of these arteries, and this was particularly true of the supraorbital and occipital arteries. To be sure, direct stimulation of these nerves was painful, but the tests referred to were all on the artery itself after it had been separated from any visible adjacent nerve trunk. Since the temporal artery has a rich anastomosis with the supraorbital and frontal arteries anteriorly and the occipital arteries posteriorly, there is reason to assume that there is also a free overlapping of the nerves supplying these vessels. Hence, even when the nerve supply of the temporal artery was blocked in the temporal region, if one of the main branches of this artery was traced far enough anteriorly or posteriorly it was again found to be sensitive, presumably because of an additional nerve supply from these areas.

The anterior and posterior arteries of the scalp, that is, the frontal, supraorbital, postauricular and occipital arteries, were found to be sensitive to crushing, burning and stretching, just as were the temporal arteries.

*Dural Arteries*—The principal dural artery is the middle meningeal, a branch of the external carotid artery which supplies all of the supratentorial dura except for the dura of the floor of the anterior fossa and that over the anterior pole of the brain. The latter dura is supplied by the anterior meningeal arteries and by branches of the internal carotid and of the ethmoidal arteries. The subtentorial dura is supplied by the posterior meningeal arteries, branches of the occipital, vertebral or ascending pharyngeal arteries.

As in the observations on the arteries of the scalp, it was demonstrated that the main trunks of all the dural arteries were sensitive to painful stimuli. The stimuli employed included faradizing, burning, distending, stroking, stretching and crushing (middle meningeal artery and its branches, 11 subjects and 96 observations [fig 3 A]). Distention was effected just as it was in testing the sensitivity to pain of the superficial temporal artery, on one occasion the tip of a clamp was introduced into the lumen of the middle meningeal artery and spread, and on another a series of silk sutures equally placed about the circumference of the artery were simultaneously pulled on (fig 3 B). The pain produced was localized fairly accurately in the area of distention and also was commonly described as being in the back of the eye. It was aching, similar to that resulting from distention of the temporal artery. It also was accompanied by nausea.

A few of the smaller branches arising from the main divisions of the middle meningeal artery, even within a few centimeters of the midline at the vertex, were found to be sensitive to pain. The area in which the pain was felt was usually fairly discrete and was somewhere in the region of stimulation. In general, the pain experienced from stimulation of the middle meningeal artery was within the homolateral temporoparietal region and was deep and aching. It could be shown that there was a slight discrepancy in the exact localization when different parts of the artery were stimulated. Thus, pain arising from the main trunk of the artery and the more proximal part of the anterior branch was felt in the midtemporal region, pain arising from the more distal divisions of the anterior branch was more parietal in its location, and pain arising from the posterior branches of the artery was localized behind both of the other two sites.

The usual experience associated with reflection of a temporoparietal osteoplastic flap was the occurrence of sharp pain in that general region as a result of stretching the middle meningeal artery or tearing it from its groove in the bone (24 subjects, 24 observations). The severity of the pain was variable but usually comparable to that from painful superficial structures and more severe than that arising from stimulation of most pain-sensitive intracranial structures. This impression was substantiated by application of other stimuli to the artery. Although distention or a



main trunk of the artery by some mechanical means repeatedly caused pain, vigorous constriction of the arterial wall after local application of epinephrine was unaccompanied by pain. These findings conformed to those made on similarly testing the superficial temporal artery.

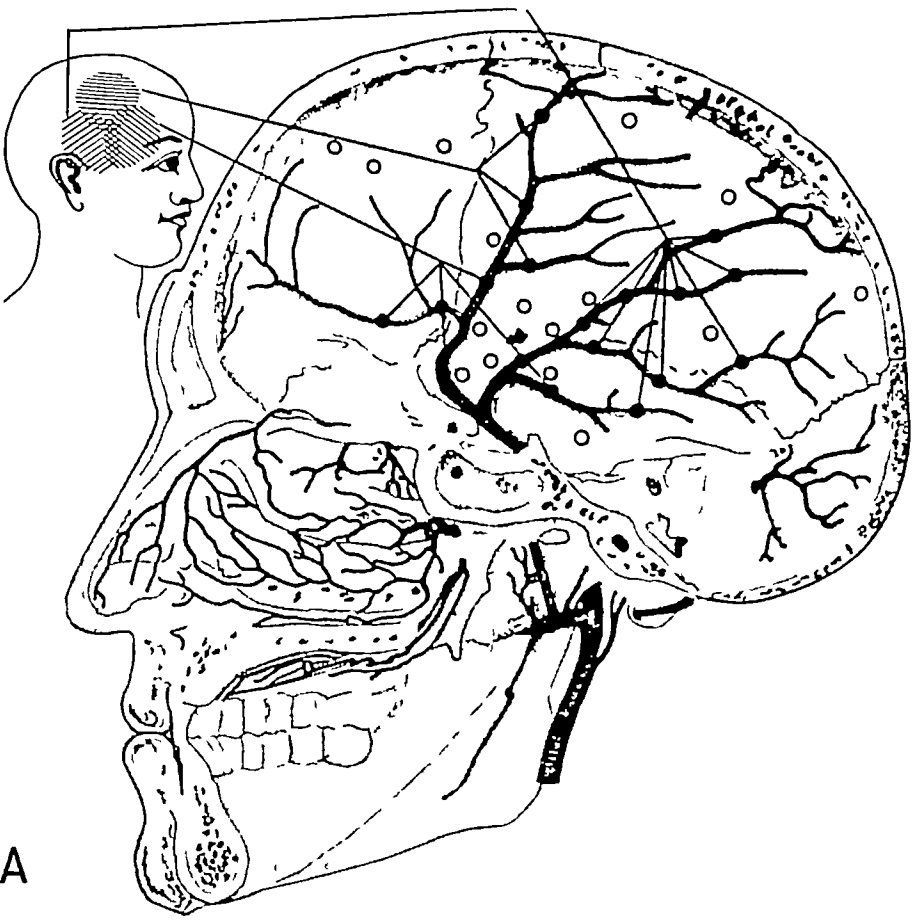
Transection, ligation or procaine hydrochloride infiltration of the midmeningeal artery anywhere along its course, even as far proximal as the foramen spinosum, was always followed by anesthesia of the artery distal to that point. This finding plus the further observation that the dura which lies between the branches of the midmeningeal artery was insensitive to pain indicates that the pain-conducting fibers join the artery near its origin and travel adjacent to it.

The localization of pain from stimulation of the anterior meningeal arteries was limited to the forehead and the region of the eye on the same side (12 subjects, 48 observations). That from the posterior meningeal arteries was limited to the back of the head on the same side (4 subjects, 16 observations). The sensitivity to pain of the anterior and posterior meningeal arteries was limited to the most proximal portions of these quickly arborizing vessels, and the small distal branches in the dura over the frontal poles of the cerebrum and over the cerebellar lobes were insensitive to pain.

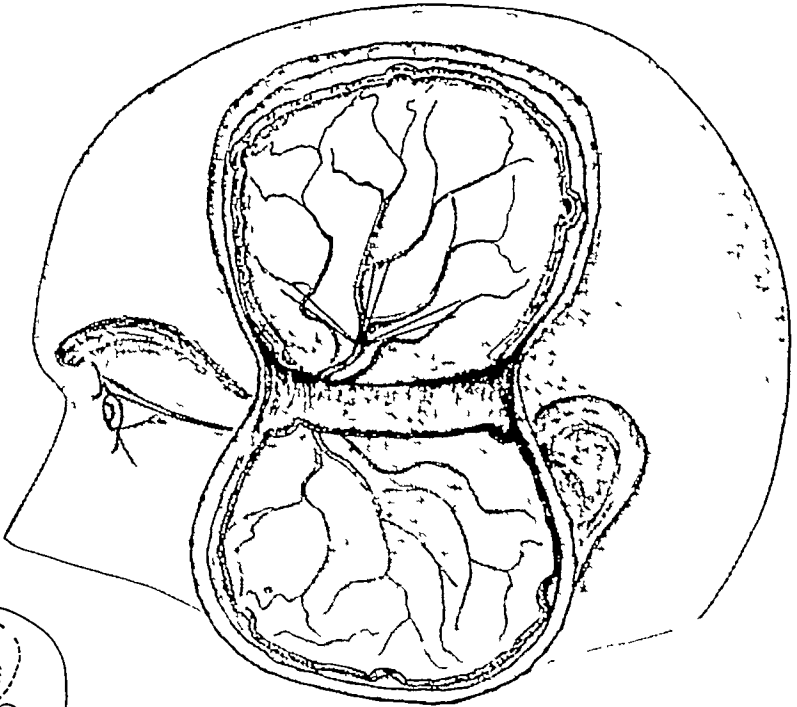
*Dura, Supratentorial*—The supratentorial dura (fig 4) covering the convexities of the cerebrum and exclusive of the base was found to be entirely insensitive to all forms of stimulation except along the margins of the dural sinuses and along the course of the middle meningeal artery (11 subjects, 148 observations).

The entire dural floor of the anterior fossa (12 subjects, 48 observations), on the contrary, while inconstantly sensitive to pressure, was almost uniformly sensitive to faradic stimulation, and the pain arising from this region was localized to the homolateral eye, that is, over, within, behind or beside the eye. Sometimes, stimulation of the floor of the anterior fossa at widely separated points caused pain at slightly different sites within the general region about the eye. The dura of the olfactory groove was found to be unusually sensitive to pain, while the dura that forms the roof of the orbit was perhaps slightly less so. The dura along the superior aspect of the sphenoidal ridge, in the region of the dorsum sellae and at the base of the anterior clinoids was but moderately sensitive. At the lateral and anterior margins of the floor of the fossa, that is, lateral and anterior to the roof of the orbit, the dura became progressively less sensitive to pain and was finally insensitive at points 2 cm or more above the floor (fig 5).

As an example of the occasional variation from the normal in the presence of a local disease process, the following experience deserves mention. The dura several centimeters above the floor of the anterior fossa was found to be sensitive in the presence of a large meningioma of this region which had a wide attachment to the dura of the floor of



A



B

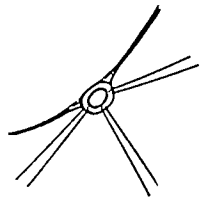


Figure 3

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this fossa and above. Furthermore, arteries over the convexity and within the substance of the tumor which had doubtless grown in from the anterior meningeal arteries were sensitive to pain. The pain arising from stimulation of these arteries and from the dura about the upper margins of the tumor's attachment was experienced in the region about the eye, just as was noted after stimulation of the normal dura and dural arteries on the floor of the anterior fossa.

It should be emphasized that, while visible portions of the dural arteries of the floor of the anterior fossa were sensitive to pain, the dura which lies between these vessels was itself sensitive to pain. The tests were made when the tissue was dry, so that spread of the stimulation was minimal. A similar arrangement was found to exist in the posterior fossa. But the same was not true for any part of the floor of the middle fossa. Here the dura was insensitive. While all the principal branches of the middle meningeal artery were sensitive to pain, the dura at all points more than 2 mm away from such vessels was insensitive to all the aforementioned forms of stimulation. The floor of the middle fossa (fig 5) was examined as far medially as the foramen lacerum and the cavernous sinus (4 subjects, 20 observations).

Stimulation of the dural capsule of the components of the fifth cranial nerve resulted in pain usually distributed over the face, and it was impossible to determine whether the nerve itself rather than its capsule was receiving the stimulus. Suffice it to say that whatever served to stimulate the capsule doubtless stimulated the nerve also.

*Dura of the Sella Turcica and Diaphragma Sellae*—There was opportunity to make observations on the dura and diaphragma of the sella only when tumors existed in the region, and in these instances the dura was more or less attenuated from distortion and compression by the tumor. Faradic stimulation of the thinned-out diaphragma in a case of pituitary adenoma failed to cause pain. Pressure on this structure and also tearing it by spreading its fibers with a clamp produced pain experienced just behind the eye, yet crushing the torn edge did not cause pain. It appeared that the pain induced by pressure and tearing was the result of distortion of the pain-sensitive carotid artery nearby (3 subjects, 20 observations).

#### EXPLANATION OF FIGURE 3

Fig 3—*A*, view of the middle meningeal artery. ○ indicates the point of stimulation of the dura without pain. ● indicates the point of stimulation causing pain. The diagram shows three overlapping areas of pain in the parietotemporal region resulting from stimulation of different portions of the artery and its branches. *B*, view of traction sutures symmetrically placed in the wall of the middle meningeal artery. The mechanical distention of the artery resulting from simultaneous traction on all three sutures caused pain in the hatched area on the diagram.

The only opportunity for studying the dura lining the sella occurred on the occasion of introduction of a suction tube into the depths of the sella or pulling with forceps on the deep fragments of a pituitary adenoma. Both of these methods of stimulation in 1 subject produced pain near the top of the head. Furthermore, if the stimulus was applied to the left side of the sella the pain was felt to the left of the midline at the vertex, the opposite was true for the other side. In this case it was known that the roof of the sphenoid sinus had collapsed, and it is possible that the membranous lining of the sinus was being stimulated and was the cause of the pain at the vertex.

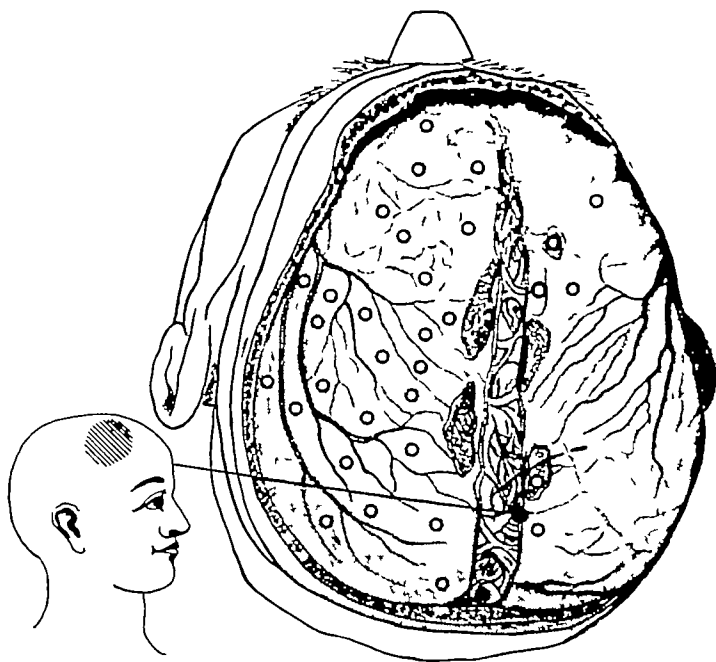


Fig 4—View of the superior sagittal sinus and the adjacent venous lacunae and arachnoid granulations. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagram shows the area of pain following stimulation of the margin of the superior sagittal sinus.

*Dura of the Posterior Fossa*—The dura over the convexity of the cerebellar hemispheres was everywhere insensitive to pain except along the margins of the occipital and transverse sinuses (6 subjects, 150 observations). The floor of the posterior fossa, on the other hand, was uniformly sensitive in a fashion comparable to that of the anterior fossa. Roughly, the floor of the posterior fossa was taken to be that more or less triangular region which lies between the rim of the foramen magnum and the lateral attachment of the tentorium cerebelli. Observations with closely spaced stimulation of the dura of this region revealed that, while the entire area was sensitive to pain, from some points the pain was felt just behind the homolateral ear, and from other points it was felt in the back of the head.

That portion of the dura which lay over or was near the margins of the lateral (sigmoid) sinus when stimulated caused pain behind the ear (2 subjects, 8 observations) Section of the ninth and tenth

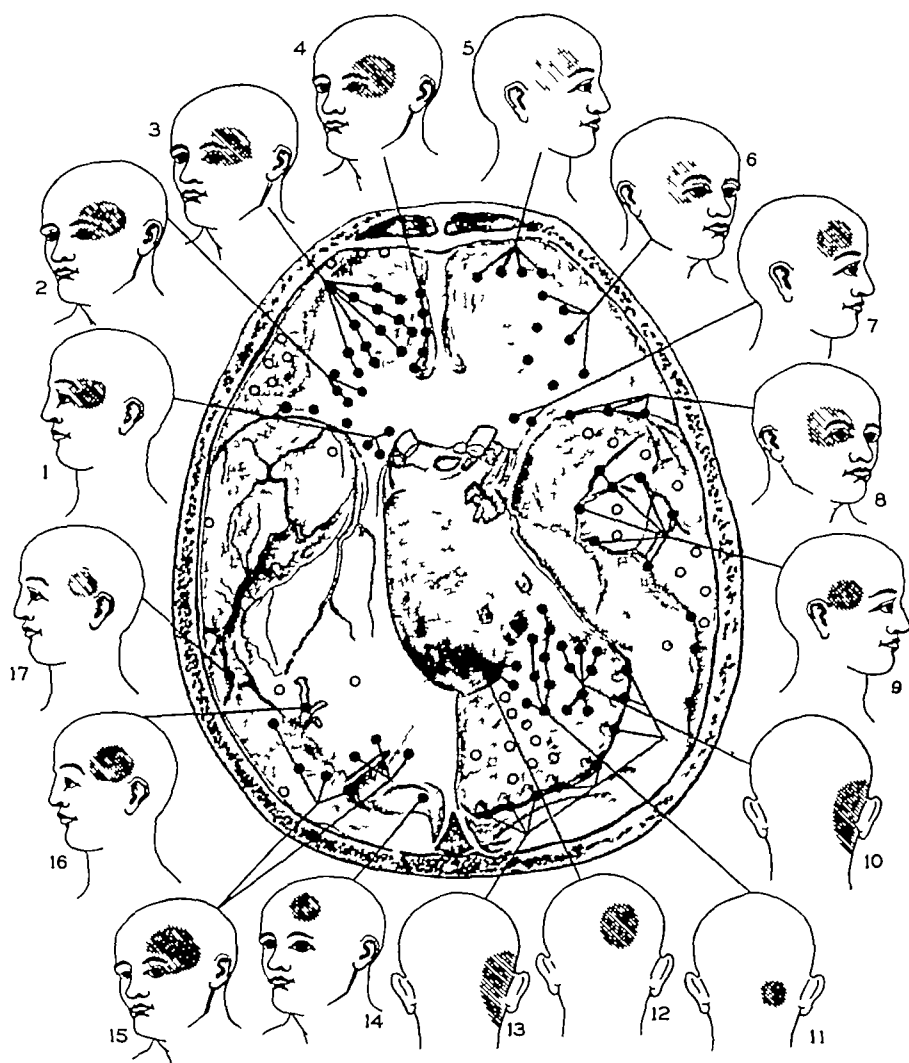


Fig 5—View of the dural floor of the skull, the tentorium cerebelli and the adjacent venous sinuses and venous tributaries ○ indicates the point of stimulation without pain ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of (1 to 8) the dura of the floor of the anterior fossa, (9 and 17) the middle meningeal artery, (10 to 12) the dura of the floor of the posterior fossa, (13) the inferior wall of the transverse sinus, (14) the superior wall of the torcular Herophili, (15) the superior wall of the transverse sinus and upper surface of the tentorium cerebelli, and (16) the inferior cerebral veins

cranial nerves in 1 of the patients made it impossible to elicit pain on subsequent stimulation of the aforementioned dural and sinal structures. Stimulation of the remaining and more mesial portion of the dura, extending to the rim of the foramen magnum caused pain low in the

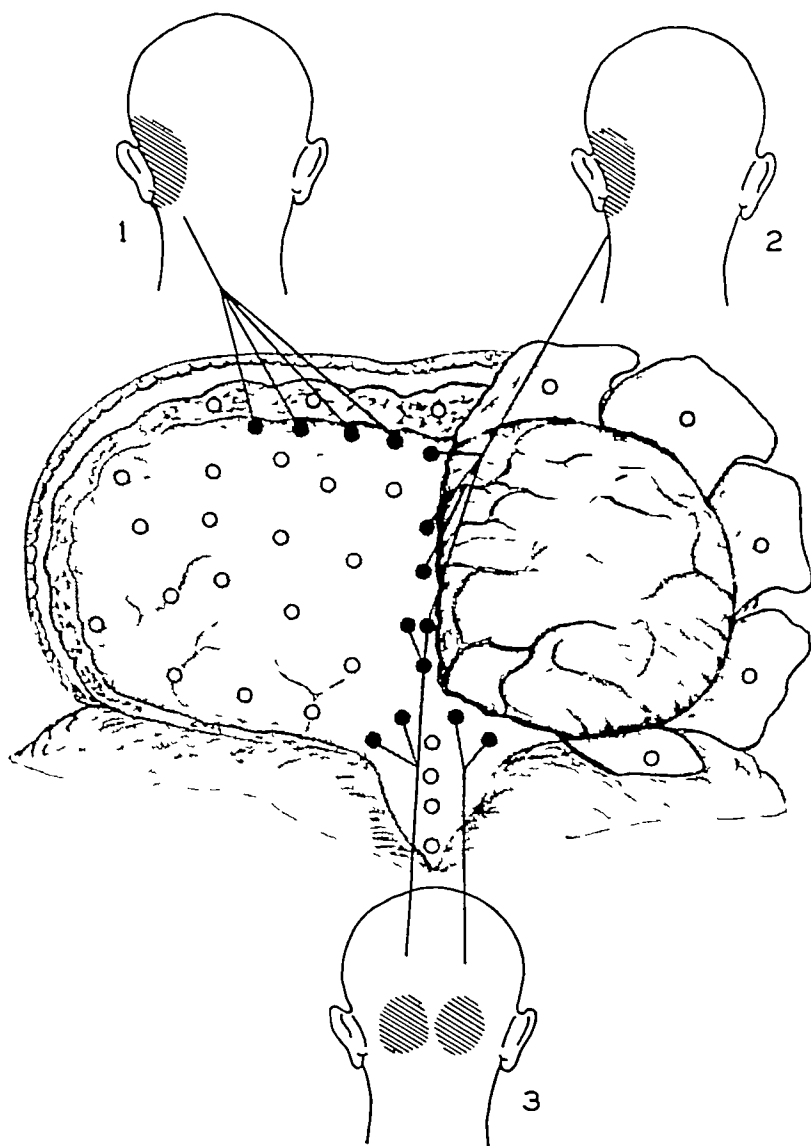


Fig 6—View of the venous sinuses and the dura over the cerebellum and the upper part of the cord ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain The diagrams show the area of pain following stimulation of (1) the transverse sinus, (2) the torcular Herophili and upper part of the occipital sinus, and (3) the lower part of the occipital sinus

back of the head (2 subjects, 14 observations) This region of the dura was sometimes seen to be traversed by small branches of the posterior

meningeal arteries, and the localization of the pain following stimulation was the same for both the dura and the arteries (2 subjects, 8 observations) Section of the posterior roots of the first three cervical nerves in one of the patients made it impossible to elicit pain on subsequent stimulation of the aforementioned dural and arterial structures There was no occasion to visualize or stimulate the dura which lies beneath the brain stem and covers the clivus blumenbachii (figs 5, 7 and 8)

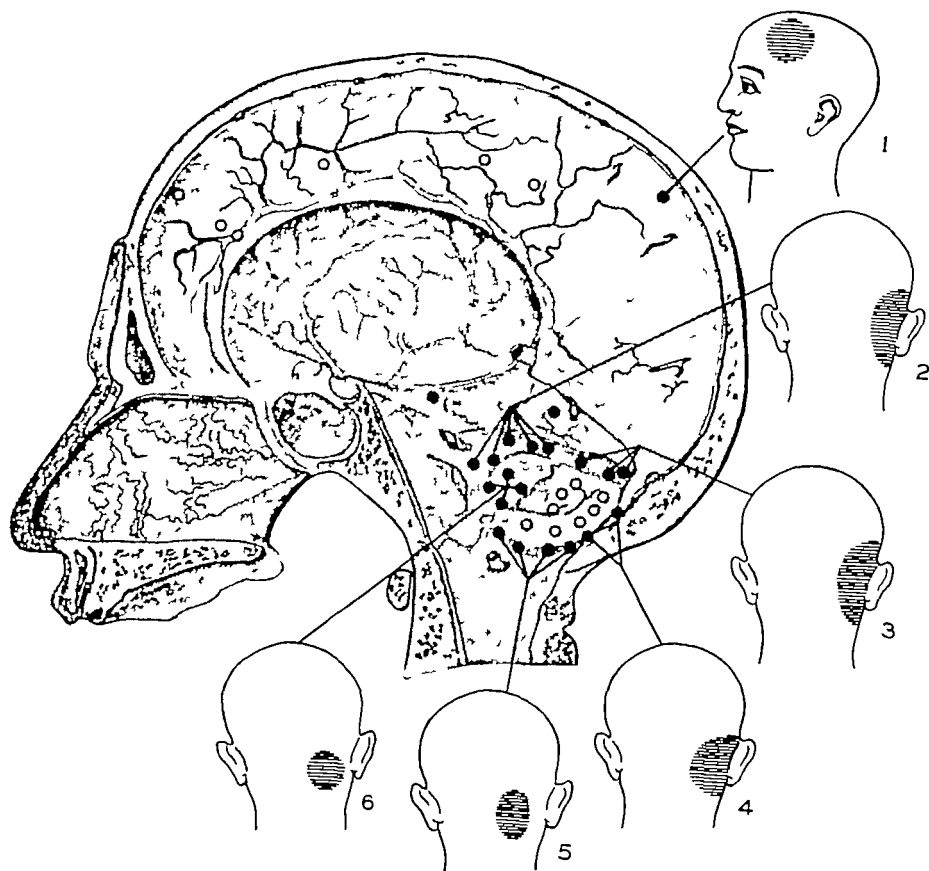


Fig 7—View of the falx cerebri, the dura and venous sinuses of the posterior fossa. ○ indicates the point of stimulation without pain ● indicates the point of stimulation causing pain The diagrams show the area of pain following stimulation of (1) the superior sagittal sinus, (2) the sigmoid sinus, (3) the transverse sinus, (4) the upper part of the occipital sinus, (5) the lower part of the occipital sinus, and (6) the dura of the floor of the posterior fossa

*Falx*—It was found that burning, cutting, faradic stimulation and pressure along the anteroposterior extent of the falx failed to produce pain unless the margins of the superior sagittal sinus were displaced or

encroached on (5 subjects, 35 observations) An exception to this general finding on the sensitivity of the falx was the observation that faradic stimulation of the first few centimeters above its attachment to the crista galli caused pain in and about the homolateral eye (2 subjects, 6 observations) There was opportunity to explore the inferior margin of the falx only along the anterior half of its border with the inferior

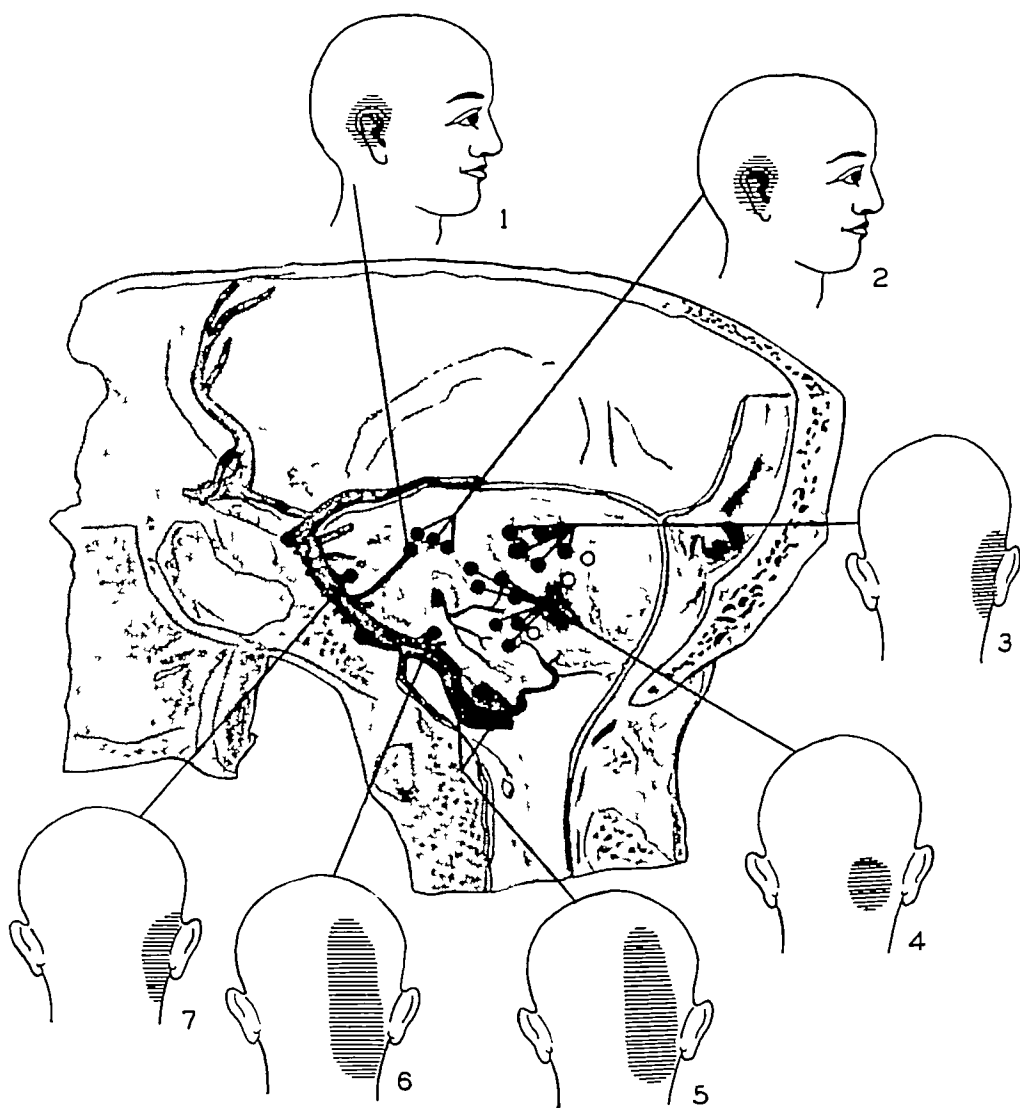


Fig 8—View of the arteries and dura of the posterior fossa. ○ indicates the point of stimulation without pain ● indicates the point of stimulation causing pain The diagrams show the area of pain following stimulation of (1) the internal auditory artery, (2) the dura at the porus acusticus, (3) the wall of the sigmoid sinus and the adjacent dura, (4) the dura near the rim of the foramen magnum, (5) the vertebral artery, (6) the posterior inferior cerebellar artery, and (7) a pontile artery

sagittal sinus, this much of it was found to be insensitive Lateral pressure against the falx with a blunt ventricular needle was exerted to a



degree sufficient almost to puncture this tough structure, without causing pain. Sometimes the point of pressure was within 2 cm of the superior sagittal sinus, yet pain did not result (figs 7 and 9)

*Tentorium Cerebelli*—On the superior surface of the tentorium it was found that pressure against its central portion caused pain in the homolateral side of the forehead and the region of the homolateral eye. Faradic stimulation of this surface in spotty areas of apparently fortuitous distribution (fig 5) caused pain in the same region (4 subjects, 20 observations)

On the inferior surface of the tentorium the findings at first appeared variable but eventually permitted inferences to be drawn. Slight or even

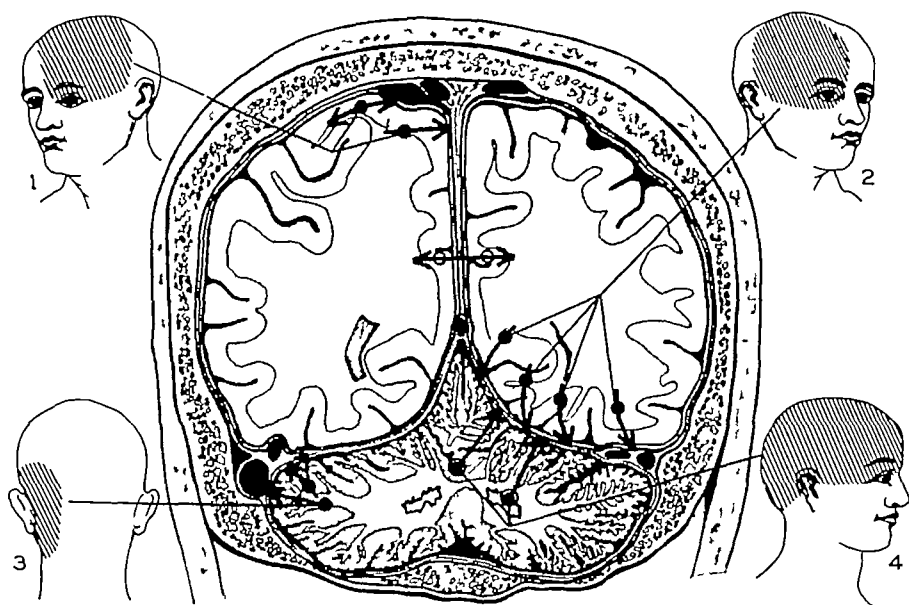





Fig 9—View of a coronal section through the head, showing the falx cerebri, the tentorium cerebelli and the associated venous sinuses.  indicates the point of stimulation of the falx cerebri without pain.  indicates the point of stimulation causing pain.  indicates the point at which stimulation of greater intensity than usual is required to produce pain. The diagrams show the area of pain following stimulation of (1) the superior sagittal sinus and tributary veins, (2) the superior surface of the tentorium cerebelli and wall of the transverse sinus, (3) the inferior wall of the transverse sinus, and (4) the inferior surface of the tentorium cerebelli, resulting in secondary effects on 2 and 3.

moderate pressure upward usually failed to cause pain unless the margins of the venous sinuses were approached, in which case pain was usually experienced behind the homolateral ear. When pressure on the center of the tentorium was increased, pain occurred behind the ear, in the region of the forehead and eye on that side or in both regions. Strong

pressure applied at a point near the free edge at the side of the pons in 1 case caused pain low in the back of the head on the same side, apparently because of secondary displacement of some other pain-sensitive structure. Faradic stimulation of sufficient intensity to induce pain in the structures with well established sensitivity to pain (figs 9 and 10) failed to cause pain when applied to points on the undersurface of the tentorium more

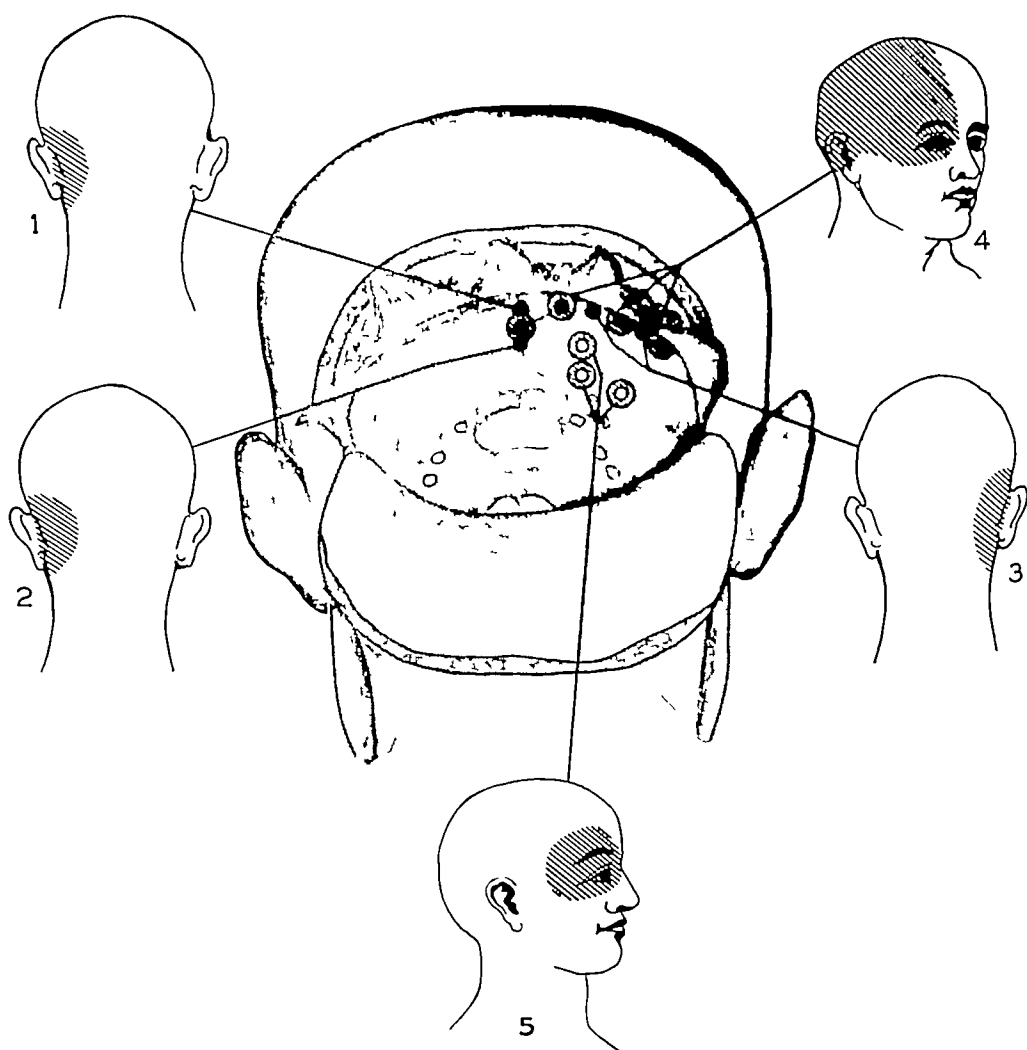


Fig 10—View of the undersurface of the tentorium cerebelli. ● indicates the point at which stimuli of usual intensity cause pain, the diagrams show the area of pain following stimulation of (1) the torcular Herophili, (2) the straight sinus, and (3) the transverse sinus. ⊙ indicates the point at which stimuli of usual intensity cause no pain whereas stimuli of increased intensity cause frontal pain, diagram 5 shows the area of pain following stimulation of the undersurface of the tentorium cerebelli. ⊙ indicates the point at which stimuli of usual intensity cause pain behind the homolateral ear whereas stimuli of increased intensity cause pain over the entire homolateral side of the head, diagram 4 shows the area of pain following stimulation of the transverse and straight sinuses.

than 5 mm from the venous sinuses. It was found further, however, that if the intensity of the stimulus was increased sufficiently pain was experienced in the forehead and in the region of the eye on that side, suggesting that the stimulus was transmitted through the tentorium to its superior surface (5 subjects, 35 observations)

*Dural Sinuses and Their Tributary Veins*—Superior Sagittal Sinus. The walls of the major extent of this sinus were found to be sensitive to pain, although in general the pain produced was only moderately intense

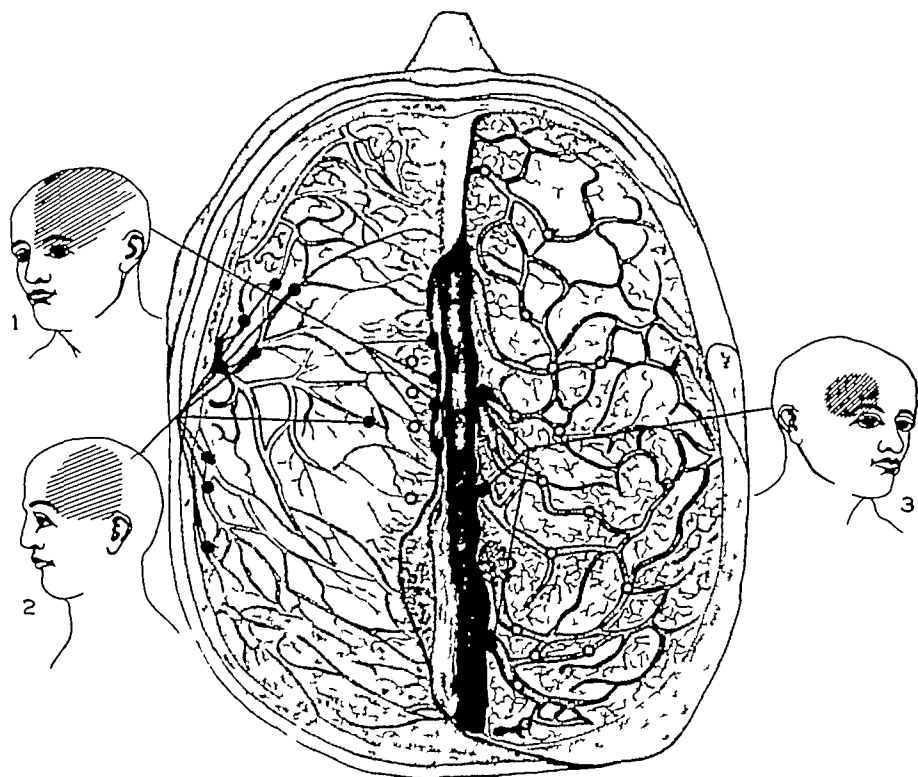


Fig 11—View with the calvarium removed. The dura and the meningeal arteries are shown on the left, the cerebral and tributary veins are shown on the right. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of (1) the margin of the superior sagittal sinus, (2) the middle meningeal artery, and (3) the tributary veins to the superior sagittal sinus.

as compared with that resulting from stimulation of the middle meningeal artery or of the large arteries at the base of the brain. Pressure, traction and faradic stimulation were used. In addition, it was discovered that stripping the dural wall away from its attachments to the cranial vault produced slight pain. In its more anterior portion, that is, along

its first 7 or 8 cm, the sinus was either insensitive or much less sensitive than in its middle and posterior thirds. Pain in the frontal part of the head and in the region of the eye usually followed stimulation of the sensitive regions. Sometimes the pain arising from the more anterior half of the sinus was localized in the parietal region, near the vertex. It was also noted, although it was impossible to define the area accurately, that the middle third of the sinus lost some of its sensitivity after an incision through the dura that traversed the main trunk of the middle meningeal artery and the nerves traveling along with the artery. The side of the head on which pain was felt (figs 4 and 11) was always the same as the side on which the wall of the sinus was stimulated (8 subjects, 32 observations).

**Tributary Veins to the Superior Sagittal Sinus (Superior Cerebral Veins)** These veins, which pass from the cerebral cortex to the sinus, were found to be insensitive to coagulation, crushing and faradic stimulation except for the few millimeters of vessel next to the sinus. However, traction on the vessels at all points along the extent of the sinus produced pain in the same sites as that caused by direct stimulation of the adjacent wall of the sinus (8 subjects, 32 observations). There was variability in the occurrence and degree of the pain resulting from traction on these veins, but sometimes, and particularly along the posterior third of the sagittal sinus, very slight traction caused moderately intense pain. With the sudden collapse of a dilated lateral ventricle, all of the veins passing from the cortex to the sagittal sinus were observed to be put on stretch, and at the same time there was pain in the homolateral frontoparietal and ocular regions (figs 4, 9 and 11).

**Pachionian Granulations and Venous Lacunae** Pachionian granulations were stimulated with faradic current without producing pain (3 subjects, 12 observations). It seemed likely that all such arachnoid extensions were insensitive. The walls of the venous lacunae at various points along the lateral margins of the sagittal sinus (fig 4) also were insensitive to burning, pressure and faradic stimulation (3 subjects, 12 observations).

**Inferior Sagittal Sinus** The inferior sagittal sinus was stimulated only along its anterior 5 to 6 cm, and in this region the channel is of smaller caliber and has few or no tributaries from the cerebrum (fig 7). When this anterior portion of the sinus was crushed or stimulated with faradic current it was found to be insensitive (4 subjects, 12 observations).

**Transverse Sinus, Torcular Herophili and Straight Sinus (Supratentorial Surfaces)** Stimulation of the walls of the transverse sinuses and torcular Herophili on their supratentorial surfaces by faradic current uniformly caused pain in the region of the homolateral side of the forehead and the homolateral eye (4 subjects, 16 observations). The stimulation that resulted from pressure and gentle friction in the same

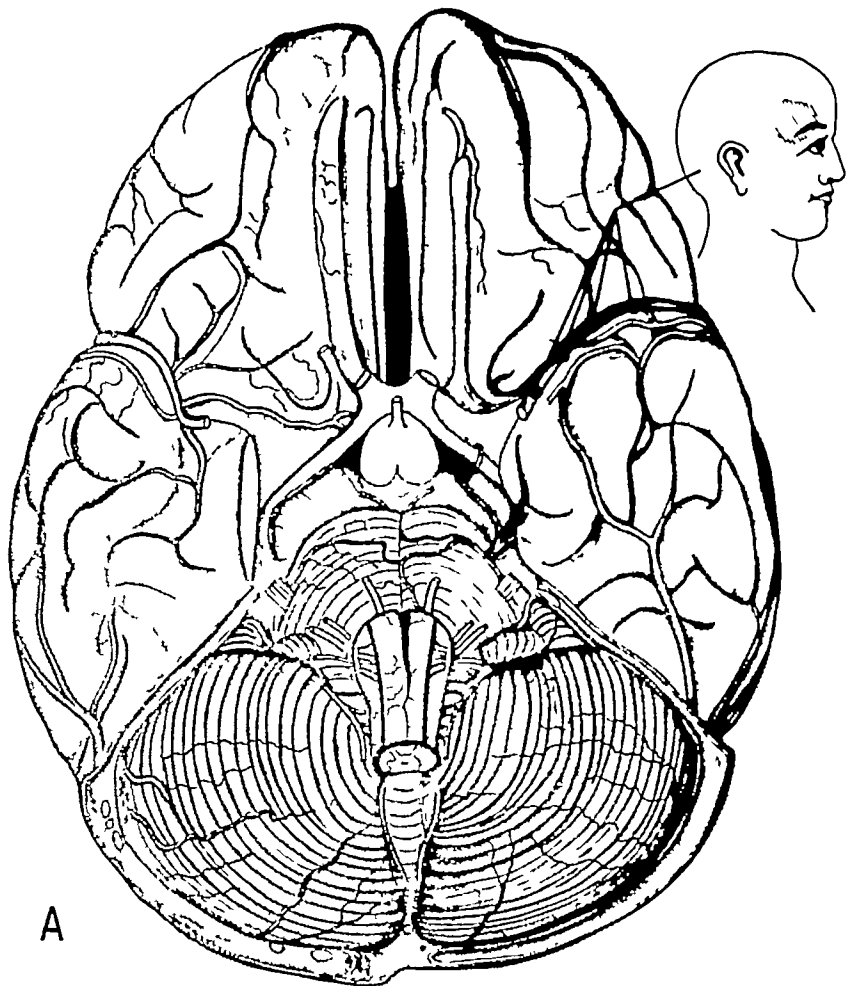
regions was insufficient to cause pain. Only a short segment of the straight sinus near the torcular was available for study (3 subjects, 6 observations). Pain resulting from stimulation was felt in the homolateral side of the forehead and the homolateral eye. It was not possible to stimulate that part near the free edge of the tentorium, nor were the veins of Galen investigated (figs 5 and 9).

**Inferior Cerebral Veins** The veins on the inferior surface of the temporal lobe were not sensitive to pain. But the main veins which pass from the undersurface of the temporal lobe to the lateral end of the transverse sinus and to the superior petrosal sinus were found invariably to be sensitive to crushing, burning, stretching and faradic stimulation. These veins, several in number and sometimes referred to as the veins of Labbe, were as long as 1.5 to 3 cm. in their extracerebral course (figs 5 and 12 A). When they were stimulated, the pain was experienced in the homolateral temporal region (3 subjects, 10 observations).

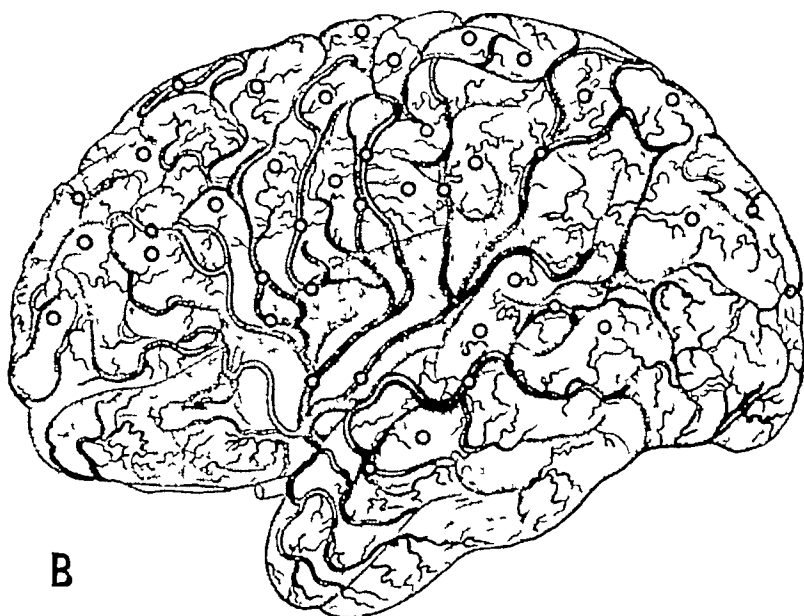
**Occipital Sinus** That portion of the sinus that lies in the midline and extends from the torcular to the rim of the foramen magnum was uniformly sensitive to faradic stimulation, and the pain was experienced in one or both of two regions of the head (figs 6 and 7). Stimulation of the sinus near the torcular caused pain behind the ear, while stimulation near the foramen magnum caused pain low in the back of the head. After section of the posterior roots of the first three cervical nerves it was impossible to elicit pain on stimulation of the sinus near the foramen magnum. Just as was the case with the other midline sinuses, the superior sagittal and the straight, the side of the head on which pain was felt was homolateral to the side on which the wall of the sinus was stimulated. The divisions of this sinus which partly encircle the foramen magnum were also sensitive, and the pain was felt low in the back of the head (4 subjects, 20 observations).

**Transverse Sinus, Torcular Herophili and Straight Sinus (Infratentorial Surfaces)** Stimulation of the walls of these sinuses on their infratentorial surfaces by faradic current uniformly caused pain in an area behind the homolateral ear (6 subjects, 24 observations). In addition, it was found that if a current of greater intensity was employed pain was also felt in the homolateral side of the forehead and near the homolateral eye. The tributary veins from the cerebellum to these sinuses were found to lack sensitivity to pain when stimulated with faradic current, crushed or put on slight traction (figs 6, 7 and 10).

The wall of the lateral portion of the transverse sinus (sigmoid sinus) was stimulated from the inside of the posterior fossa (figs 5, 7 and 8). The margins of the sinus here are indistinct, but faradic stimulation of the dura overlying the sinus, from the margin of the tentorium to the jugular foramen, uniformly caused pain behind the homolateral ear (see section on the dura of the posterior fossa).



A



B

Fig 12—*A*, view of the veins at the base of the brain ● indicates the point of stimulation causing pain The diagram shows the area of pain following stimulation of the deep segment of the sylvian vein *B*, view of the arteries over the cerebral cortex ○ indicates the point of stimulation without pain

The wall of the cavernous sinus in 1 subject was stimulated at the point where the midcerebral vein joined it. Faradic stimulation here caused pain in the homolateral ocular and maxillary region. Since the ophthalmic and maxillary nerves lie in the lateral wall of the sinus, it is probable that they were being stimulated directly.

There was no opportunity to stimulate directly the more inaccessible venous channels, which include the petrosal sinuses and the basilar plexus.

*Pia-Arachnoid*—The pia-arachnoid covering the convexity of the cerebral and cerebellar hemispheres was found to be insensitive to crushing, burning, stretching and faradic stimulation, with the possible exception of the pia-arachnoid very near to the great arteries at the base of the brain (30 subjects, 120 observations). It was found that tearing the pia-arachnoid surrounding the carotid arteries and the anterior part of the circle of Willis caused subjects to complain of pain, but this might well have been the result of secondary pull on these sensitive arteries (figs 12 *B* and 13 *A*). The arachnoid forming the roof of the cisterna magna was found to lack sensitivity to pain (4 subjects, 12 observations).

*Arteries and Veins of the Brain*—The pial arteries and veins over the superior and lateral convexities of the cerebrum (24 subjects, 300 observations) and the cerebellum (16 subjects, 150 observations) were found to lack sensitivity to pain with all forms of stimulation (figs 12 *B* and 13 *A*).

However, as will be described, when pain resulted from stimulation of certain cerebral and pial arteries at the base, it was deep, intense, dull and aching. It was diffuse, yet grossly localizable, and it became throbbing when the stimulus was repeated. The pain, when prolonged, was associated with a feeling of nausea. When different pain-sensitive arteries were stimulated, the quality and intensity of pain that ensued were approximately of the same order, but the sites varied, as will be described.

The intracranial segment of the internal carotid artery was consistently sensitive to stretching, stroking and faradic stimulation (3 subjects, 10 observations). The pain was felt behind the eye and low in the temporal region on the same side (fig 13 *B*).

The middle cerebral artery was found to be similarly sensitive along its proximal 1 to 2 cm (3 subjects, 10 observations). Distal to this region, where the artery lies hidden in the lateral cerebral fissure and where it courses over the parietal lobe, it was not sensitive (20 subjects, 60 observations). Pain arising from the proximal segment had the same distribution in and behind the eye as did that from the internal carotid artery.

The anterior cerebral artery was found to be sensitive to crushing, stretching, burning and faradic stimulation from its point of origin to a point 1 cm beyond the genu of the corpus callosum, a segment several

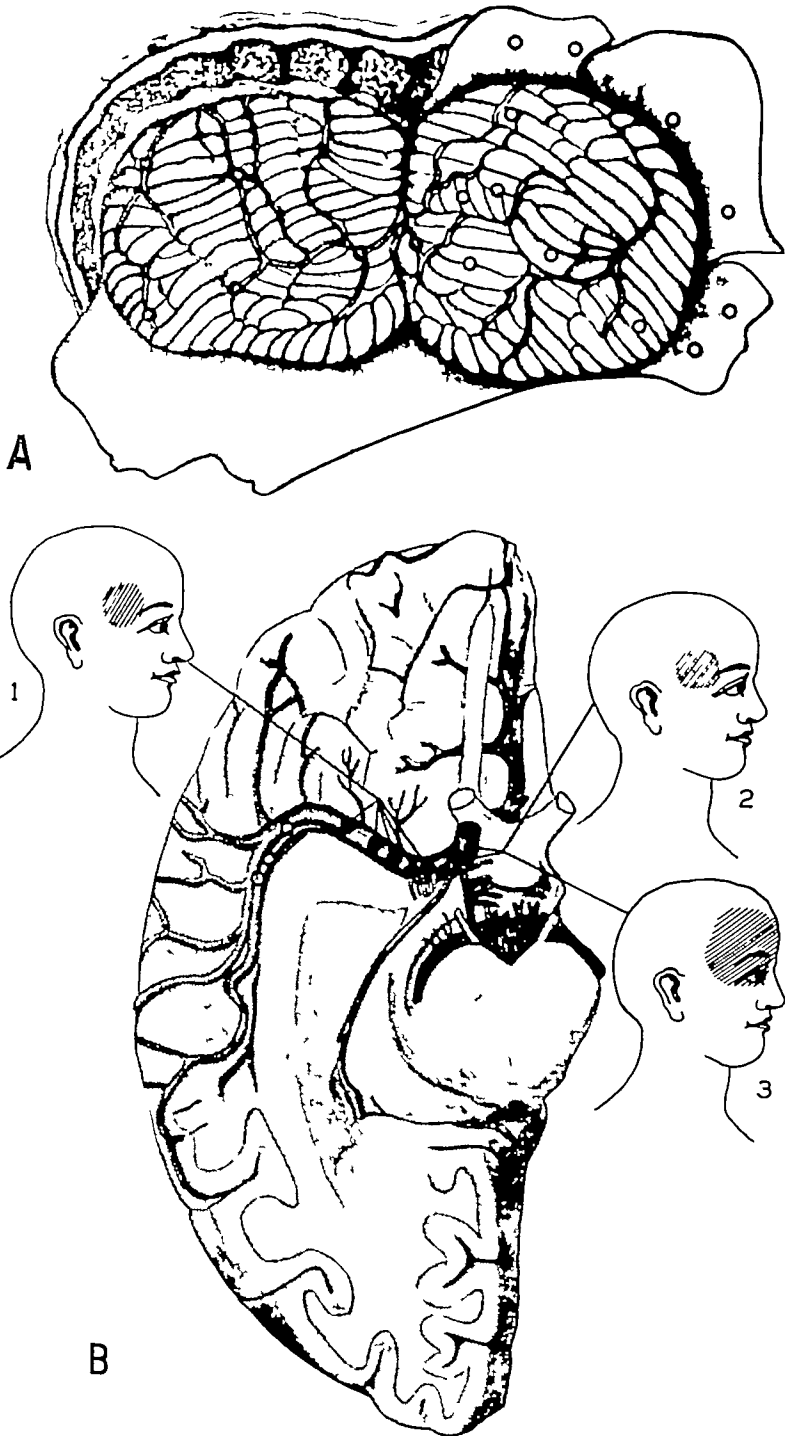


Fig 13—*A*, view of the arteries and veins over the cerebellar cortex. ○ indicates the point of stimulation without pain. *B*, view of the intracranial portion of the internal carotid artery and the proximal part of the middle cerebral artery. ○ indicates the point of stimulation without pain. ● indicates the point of stimulation causing pain. The diagrams show the area of pain following stimulation of (1) the middle cerebral artery and (2 and 3) the intracranial portion of the internal carotid artery.



centimeters in length (3 subjects, 12 observations) Beyond this point the artery was insensitive The pain arising from the proximal segment was experienced in a rather poorly localized area behind and above the homolateral eye (fig 14 *A*)

One of the principal pontile arteries at a point about 1.5 cm from its origin (figs 8 and 14 *B*) was found to be sensitive to pain on crushing, traction, coagulation and faradization, and the resulting pain was experienced behind the homolateral ear (1 subject, 4 observations)

The internal auditory artery, which accompanies the seventh and eighth cranial nerves (figs 8 and 14 *B*), was sensitive to stretching and faradic stimulation, and the pain was experienced in and just behind the homolateral ear (2 subjects, 8 observations)

The posterior-inferior cerebellar artery was sensitive to faradic stimulation and stretching in the proximal 1 to 2 cm of its course (2 subjects, 8 observations), beyond this it was insensitive (6 subjects, 20 observations) The pain arising from the proximal segment was felt in a rather diffuse area in the homolateral occipital and suboccipital regions (figs 8 and 14 *B*)

The vertebral artery, when stimulated by crushing, traction and faradic current, was sensitive to pain The pain was slightly more intense but had the same distribution as that following stimulation of the posterior inferior cerebellar artery (figs 8 and 14 *B*), that is, in the homolateral side of the occiput and subocciput (1 subject, 5 observations)

Traction on numerous arteries at the base of the brain occurred when there was displacement of the brain stem by retraction during the removal of angle tumors The pain associated with this maneuver was widespread but for the most part was experienced on the side of the head where vessels were being stretched The pain associated with traction on the circle of Willis and its branches after distention of the third ventricle will be discussed later (see section on the third ventricle)

The middle cerebral vein, or sylvian vein, which runs in the lateral cerebral fissure to the cavernous sinus, was found on faradic stimulation to be uniformly sensitive to pain in the 3 to 4 cm nearest the sinus but inconstantly sensitive higher In 1 subject the vein was sensitive to pain well up on the lateral aspect of the brain Retraction of the temporal lobe for the purpose of exposing the segment of the vein near the cavernous sinus did not put the vein on obvious traction, since it was rather closely adherent to the frontal lobe, the effect of traction on the vein was therefore not ascertained The pain following stimulation of all sensitive points (fig 12 *A*) was felt in the anterior temporal region and in the outer angle of the brow on the same side (4 subjects, 20 observations)

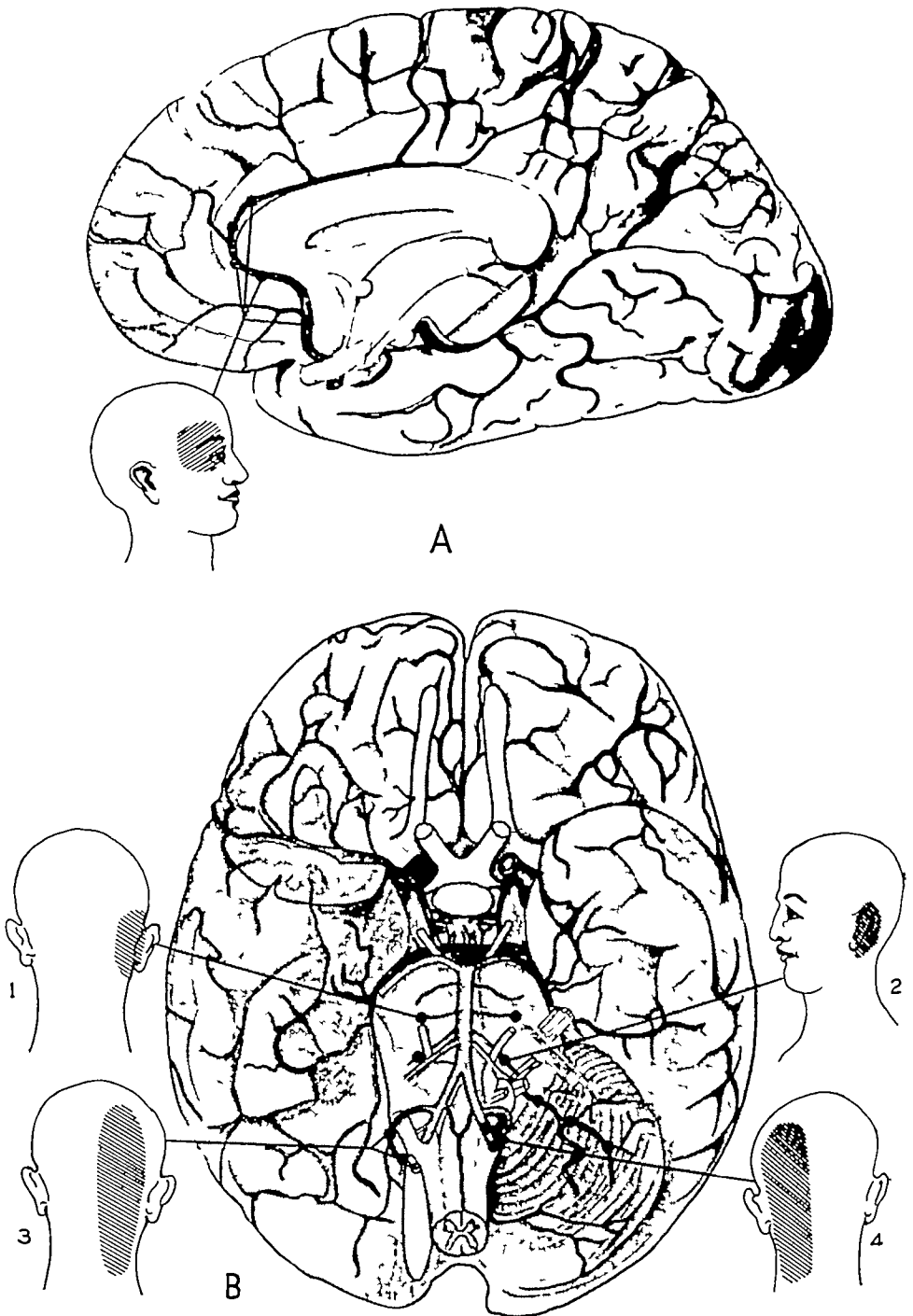


Fig 14—*A*, view of the anterior cerebral artery ● indicates the point of stimulation causing pain The diagram shows the area of pain following stimulation of the proximal segment of the artery *B*, view of the arteries at the base of the brain. ○ indicates the point of stimulation without pain ● indicates the point of stimulation causing pain The diagrams show the area of pain following stimulation of (1) a pontile artery, (2) the internal auditory artery, (3) the proximal portion of the posterior inferior cerebellar artery, and (4) the vertebral artery

*Parenchyma and Nerves*—The entire parenchyma of the cerebrum and cerebellum, including the vessels found in it, was insensitive to all forms of stimulation (30 subjects) The olfactory, optic and auditory nerves were not sensitive to pain

The cranial ninth and tenth nerves were each found, when stimulated, to cause pain behind the homolateral ear and in the throat Stimulation of the eleventh cranial nerve caused pain low in the back of the head and in the upper cervical region on the same side Stimulation of an inconstantly present posterior root of the first cervical nerve caused

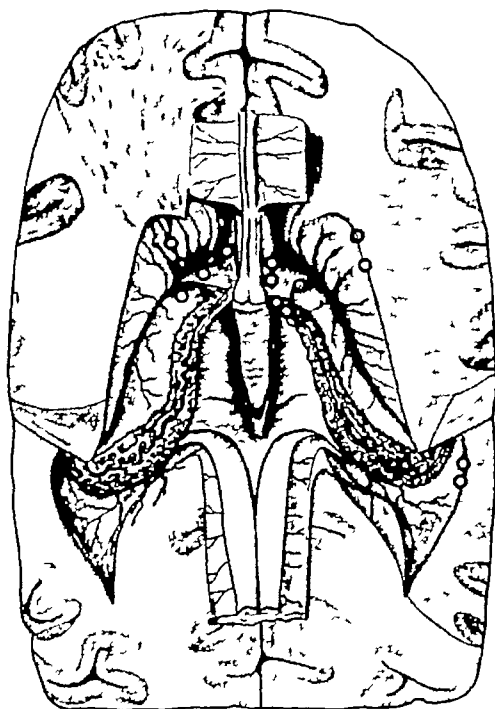


Fig 15—View of the lateral ventricles, the terminal veins, the choroid plexuses and the foramens of Monro ○ indicates the point of stimulation without pain

pain near the vertex of the head, while stimulation of the second and third posterior roots caused pain at the vertex and back of the head and neck

*Ventricles, Aqueduct of Sylvius and Choroid Plexuses*—Lateral Ventricles Although sudden collapse and overdistention of the lateral ventricles produced pain, direct stimulation of various parts of the ventricular walls (with their vessels as well as the choroid plexuses) did not result in pain Specifically, it was found that coagulation, compression and faradic stimulation of the ependymal lining of the entire

lateral ventricle produced no pain. The large terminal vein which passes along the floor of the body of the lateral ventricle was insensitive to crushing, coagulation and faradic stimulation. The same was true for the choroid plexus at the glomus and in the region of the foramen of Monro. Spreading the lumen of the foramen of Monro and cutting its margins with the endothermy were painless. Firm pressure against the part of the ventricular wall nearest the thalamus was not followed by pain (4 subjects, 24 observations).

That a bilateral and diffuse type of headache resulted from rapid emptying or overdistention of the ventricular system was repeatedly

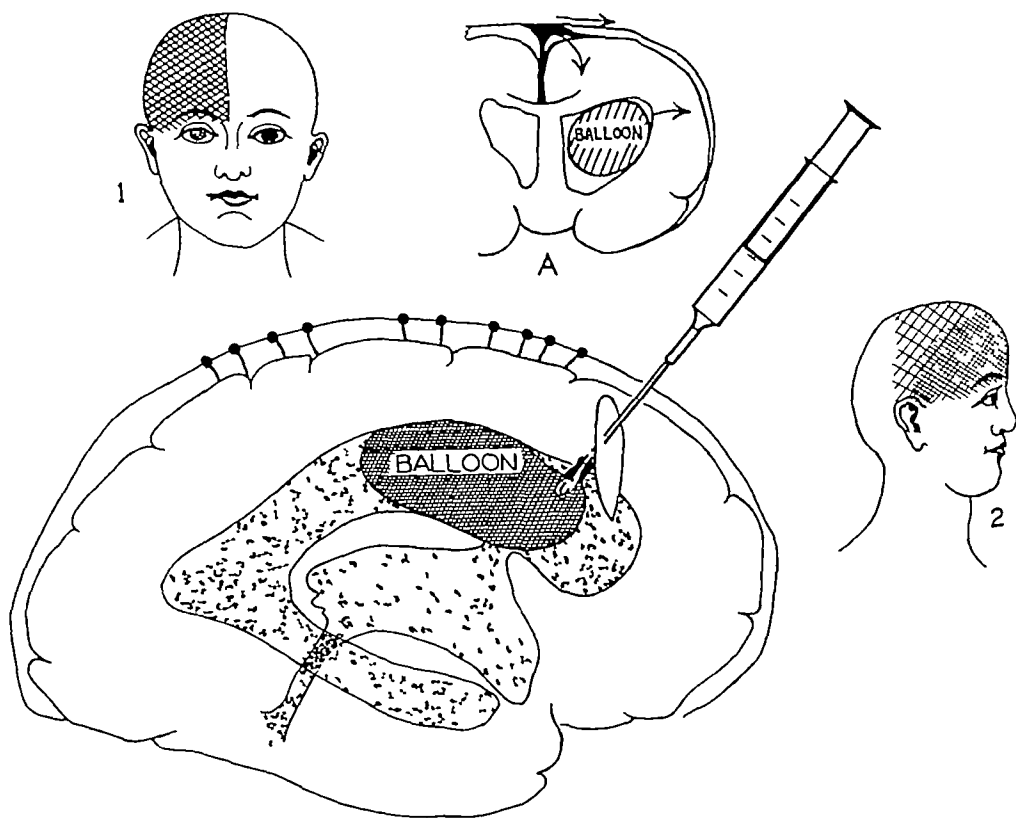


Fig 16—Schematic representation of a balloon in the lateral ventricle and the tributary veins passing from the cerebral cortex to the superior sagittal sinus. ● indicates the point at which the tributary veins were put on traction, causing pain with both inflation and deflation of the balloon. The insert (A) demonstrates the outward traction on the tributary veins, with inflation of the balloon, and the downward traction, with deflation. The diagrams, 1 and 2, show the area of pain resulting from both distention and collapse of the body and frontal horn of one lateral ventricle.

demonstrated during ventriculographic studies. In the case of a tumor filling the third ventricle, the changes in pressure of the lateral ventricles alone produced the same type of pain.

A balloon placed through a small opening into the anterior horn and body of a lateral ventricle when inflated sufficiently to cause over-distention of the ventricle produced a diffuse frontal pain on the homolateral side of the head. This was done with the brain exposed, so that there was no possibility of stretching or compressing the dural arteries. Sudden deflation of the balloon produced a transitory and intense but poorly localized pain, again over the frontal area of the same side (figs 15 and 16)

**Third Ventricle** Manipulation of a paraphysial cyst lying in the third ventricle and traction and coagulation of its stalk in the region of the roof of the ventricle all were painless. The choroid plexus of this ventricle also was not sensitive to coagulation

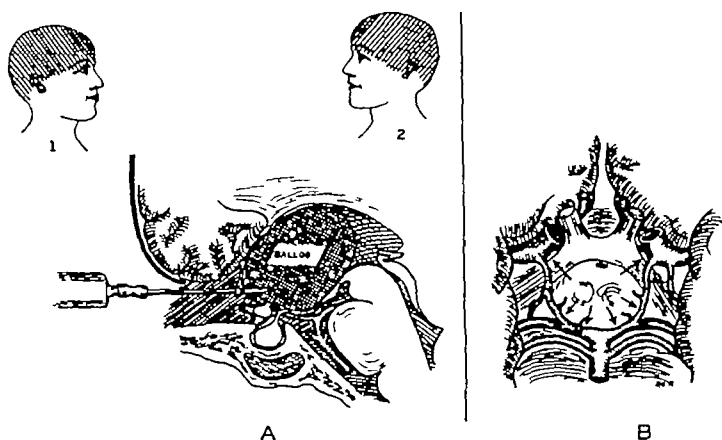


Fig 17—Schematic representation of (A) an inflated balloon in the third ventricle and (B) the resulting traction on pain-sensitive arteries of the circle of Willis. The arrows indicate the lines of force, with distention of the ventricular floor. Diagrams 1 and 2 show the diffuse area of pain following inflation of the balloon.

In a case of hydrocephalus due to obstruction of the aqueduct of Sylvius, an opening made into the third ventricle through the lamina terminalis was unaccompanied by pain. Cutting, crushing and coagulation of the ependyma of the ventricular wall here were painless. A balloon introduced into the third ventricle through this opening was inflated under moderate pressure and caused a diffuse pain over all parts of the head, variously said to be most intense in the back of the head, in the forehead and eyes and in the ears. Release of the pressure was accompanied by prompt cessation of the pain. In this respect it was unlike the pain which came with both distention and deflation of the balloon in the lateral ventricle. Pressure from the inside on the floor of the third ventricle, behind the chiasma, produced pain of similar

distribution and nature to that following distention of the ventricle, yet cutting and stretching of the floor alone in this region produced no pain. The conclusion was that the pain accompanying distention of the ventricle was due to traction by displacement of the large arteries in the region of the circle of Willis (fig 17)

**Aqueduct of Sylvius** The ependymal walls of the aqueduct were found to be insensitive when a snugly fitting catheter was used to stimulate them by pressure, stretching and traction. All parts of the walls of the aqueduct from the fourth to the third ventricle (fig 18) were thus explored (1 subject, 4 observations)



Fig 18—View showing the aqueduct of Sylvius, the fourth ventricle, the choroid plexus and the cisterna magna. ○ indicates the point of stimulation without pain

**Fourth Ventricle** The ependymal walls of this ventricle lack sensitivity to pain just as do those of the other ventricles. It was found that cutting, coagulating and cauterizing the roof of the ventricle caused no pain. Manipulation, traction and stroking of the floor of the ventricle likewise was painless (4 subjects, 16 observations). The choroid plexuses of this ventricle (fig 18) were insensitive to coagulation, crushing, traction and faradic stimulation (4 subjects, 16 observations)

#### COMMENT

This study does not purport to determine whether structures found to be sensitive to pain on stimulation actually possess sensory endings or are only traversed by pain-conducting fibers. This differentiation is

difficult at best even with histologic methods, and conclusions must be deferred. Thus McNaughton,<sup>6a</sup> who failed to find nerve endings in the walls of venous sinuses in man, indicated that the question of their presence "may well be a problem of adequate staining methods." Also, it is conceivable that the methods of stimulation employed may not have been adequate in every instance to stimulate sensory endings for pain. In this respect a specific instance, particularly important to consider, is that of the pial arteries over the convexity of the hemispheres, which were found to be insensitive. It may be that the stimulus used was inadequate at one point or was not widespread enough to stimulate sparsely distributed end organs.

1 "*Pain Pathways of the Head*"—The sensory innervation of the extracranial structures will not be considered here. A discussion of the innervation of pain-sensitive intracranial structures readily falls into a consideration of (a) the structures supplied by the fifth cranial nerve and (b) those supplied by other nerves. The fifth<sup>4</sup> and the tenth cranial nerves are widely conceded to be the principal afferent nerves of the intracranial structures, but, in addition, the ninth, eleventh and twelfth cranial<sup>8</sup> and the upper cervical nerves<sup>4</sup> play a role, as, perhaps, do other cranial nerves as well.

a The sensory fibers of the fifth nerve supply the superior surface of the tentorium cerebelli and all the pain-sensitive structures that lie above it. The subtentorial structures probably receive few, if any, fibers from the fifth nerve.

Many fibers of the fifth nerve accompany the middle meningeal artery and its branches. The "nervus spinosus" described by Luschka<sup>8c</sup> as a branch of the third division and the "nervus meningeus medius" described by Arnold<sup>9</sup> as a branch principally of the second division of the trigeminal nerve are fairly constant. But McNaughton<sup>6a</sup> has indicated that there are also fine unnamed branches of all divisions of the fifth nerve accompanying the artery. It is hardly possible or even necessary to attempt to allocate all of these fine connections to one of the three divisions, suffice it to say that they are all components of the fifth nerve.

The nerve fibers follow the main divisions of the middle meningeal artery and form a network in the adventitia. Branches of the nerves

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8 (a) Hovelacque, A. *Anatomie des nerfs craniens et rachidiens et du système grand sympathique*, Paris: Gaston Doin & Cie, 1927. (b) Pearson, A. A. The Hypoglossal Nerve in Human Embryos. *J. Comp. Neurol.* **71** 21, 1939. (c) von Luschka, H. *Die Nerven in der harten Hirnhaut*, Tübingen: H. Laupp, 1850. Fay,<sup>9g</sup>

9 Arnold, F. *Handbuch der Anatomie des Menschen*, Freiberg, A. Emmerling und Herder, 1851.

have been seen to extend out into the dura, away from the artery. The failure to find the dura itself sensitive to pain suggests that either the nerve fibers and endings are sparsely distributed or that such nerves as the dura possesses include no pain-conducting fibers. The nerves diminish in number as the vessels divide, but occasionally arteries of small caliber near the sagittal sinus have been found sensitive to pain. It is likely that some of the fibers extend even to the sagittal sinus and form a part of its sensory supply, particularly in its middle third.

There is less certainty about the nerves to the anterior meningeal arteries and the dura of the anterior fossa, but it is probable that the anterior meningeal branch of the internal carotid artery is accompanied by fibers which connect directly with the first division of the fifth nerve near the gasserian ganglion.<sup>6n</sup> It is also probable that the meningeal branches of the ethmoidal arteries are accompanied by nerves which pass through the cribriform plate as branches of the intraorbital portion of the ophthalmic nerve.<sup>6n</sup> Whereas the sensory tests indicate that the pain-conducting fibers accompanying the middle meningeal artery do not supply any part of the dura traversed by that artery, the facts that the dura of the floor of the anterior fossa is uniformly sensitive to pain and that the quality and site of reference of pain are identical suggest that it and its arteries have a common nerve supply.

The *nervus tentorii*, a branch of the first division of the trigeminal nerve, was first described by Arnold<sup>9</sup> in 1851, and its existence has been repeatedly verified since. This nerve is made up of afferent fibers from at least the posterior extent of the superior sagittal sinus, passing by way of the falx to join afferent fibers from the superior surface of the tentorium cerebelli, the superior walls of the transverse and the straight sinuses and the torcular Herophili. The collected fibers pass anteriorly from the margin of the tentorium, in or close to the sheath of the trochlear nerve,<sup>6n</sup> to join the first division of the fifth nerve about 1 cm from its ganglion. The *nervus tentorii*, therefore, carries painful impulses from the general region of the posterior and medial aspects of the supratentorial fossa.

The same nerve (*nervus tentorii*) in all probability supplies the pain-sensitive venous tributaries from the parietal and occipital lobes to the venous sinuses, but by virtue of the different location of the pain following stimulation of the group of inferior cerebral veins that drain the temporal lobe it is suggested that these latter tributary veins have another innervation, perhaps from fibers that accompany the posterior branch of the middle meningeal artery.

The arteries of the brain, including the parenchymal branches and also the choroid plexuses, have been shown to be equipped with nerve



fibers and endings<sup>10</sup> Even though Huber's<sup>10b</sup> original conception of the myelinated fibers as sensory and the unmyelinated as vasomotor must now be modified, it is conceivable that many of these are pain-conducting fibers Under the conditions of these investigations, however, stimulation of the large arteries at the base of the brain and only the most proximal portions of their cerebral branches caused pain The nerve plexuses about these larger arteries are said to have connections with various cranial nerves<sup>11</sup> (the third, the fifth, the sixth, the seventh, the eighth, the ninth, the tenth, the eleventh and the twelfth) It seems unlikely that all of these cranial nerves serve as pathways from the pain-sensitive vessels, but at present definite information about these afferent pathways for pain is limited

Studies on experimentally induced "histamine headache" indicate that the fifth cranial nerve is undoubtedly the chief afferent nerve for headache arising from dilatation of the pial and cerebral arteries of the supratentorial fossae<sup>4</sup> It is also clear that stimulation of the intracranial portion of the internal carotid artery, the proximal 1 or 2 cm of the midcerebral and postcerebral arteries<sup>12</sup> and the anterior cerebral artery as far up as the genu of the corpus callosum results in pain in the region of the homolateral eye Since the pain resulting from stimulation of these larger arteries of the forebrain is experienced in the region of the eye, there is further reason to assume that at least the major part of the innervation of these vessels is by the fifth cranial nerve

*b* The arrangement of nerves beneath the tentorium is more complicated, but a few inferences regarding pathways for pain seem justifiable The ninth, tenth and eleventh cranial nerves were shown to be sensitive to pain on direct stimulation intracranially, and the pain was

10 (a) Gulland, L The Occurrence of Nerves on Intracranial Blood Vessels, *Brit M J* **2** 781, 1898 (b) Huber, G C Observations on the Innervation of the Intracranial Vessels, *J Comp Neurol* **9** 1, 1899 (c) Stohr, P Ueber die Innervation der Pia Mater und des Plexus Chorioideus des Menschen, *Ztschr f d ges Anat* **63** 562, 1922 (d) Hassin, G B The Nerve Supply of the Cerebral Blood Vessels Histologic Study, *Arch Neurol & Psychiat* **22** 375 (Aug) 1929 (e) Stohr, P J Nerves of the Blood Vessels, Heart, Meninges, Digestive Tract and Urinary Bladder, in Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc., 1932, vol 1, sect 8, p 383 (f) Penfield, W Intracerebral Vascular Nerves, *Arch Neurol & Psychiat* **27** 30 (Jan) 1932 (g) Chorobski, J, and Penfield, W Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on Pial and Intracerebral Vascular Plexus *ibid* **28** 1257 (Dec.) 1932 (h) Clark, S L Innervation of the Choroid Plexus and the Blood Vessels Within the Central Nervous System, *J Comp Neurol* **60** 21, 1934

11 Dowgjallo, N D Beiträge zur Lehre von der Innervation des peripherischen Blutgefäß-systems, *Ztschr f d ges Anat* (pt 1) **97** 9 1932 McNaughton<sup>10a</sup>

12 Fay<sup>10c</sup>

telt in the general region of the back of the head and subocciput, the twelfth cranial nerve is said to be similar in this regard <sup>10</sup>. The studies with experimentally induced "histamine headache" indicate that the ninth and tenth cranial and upper cervical nerves are undoubtedly the chief afferents for headache resulting from dilatation of pial and cerebral arteries of the infratentorial fossa <sup>1</sup>. Further differentiation of the specific innervation of the structures is afforded by the observation that the area of pain following stimulation of the undersurfaces of the transverse sinus, the torcular Herophili, the straight sinus, the upper end of the occipital sinus and the dura in the region of the sigmoid sinus is largely in and behind the homolateral ear and in the same area after direct stimulation of the ninth and tenth nerves. Since in this region pain could not be elicited on stimulation of the aforementioned structures after section of the ninth and tenth cranial nerves, the deduction that these two cranial nerves include afferent fibers for pain from these structures is further supported.

Similarly, it is inferred that the upper cervical nerves possess fibers for pain from the lower part of the occipital sinus, the vertebral and posterior inferior cerebellar arteries, the posterior meningeal artery and the dura of the floor of the posterior fossa near the rim of the foramen magnum, since stimulation of the structures after section of the upper cervical nerves did not elicit pain.

Finally, it is to be emphasized that the innervation by sensory fibers of all the structures investigated is strictly unilateral. The line of demarcation is sharp, so that even structures in the midline have half their innervation from one side and half from the other.

2 *The Mechanisms of Headache*—From these data, inferences concerning headache may be formulated. Inflammation, traction, displacement and distention of pain-sensitive structures are the disturbances primarily responsible for headache. It is noteworthy that as a source of pain the cranial vascular structures far outweigh in number and distribution all others. It is to be anticipated, therefore, that vascular structures will often be implicated. Yet it is obvious that no single structure or mechanism is entirely responsible for the headache. Hence, the following varieties of mechanisms are briefly presented.

a Traction on veins that pass to the sagittal and transverse sinuses from the cerebral cortex results in a dull, aching pain over a wide area on the front, top and side of the head. Not only are most of these veins sensitive to pain at the site of juncture with the sinus, but secondary traction on the walls of the sinuses to which they are attached causes pain. Since many of these veins bridge a gap of 1 to 3 cm. between the cortex of the brain and the sinus, swelling of the brain puts them under tension. Hence, tumors of the brain may produce headache either by displace-

ment and direct traction on these veins or through secondary hydrocephalus. Unusually low intracranial pressure, e. g., after lumbar puncture, may similarly result in traction on the tributary veins, principally those to the sagittal sinus, and thus induce headache. Air in the subarachnoid spaces after pneumoencephalographic procedures may likewise produce headache by causing traction on these anchoring veins.

b Traction on the middle meningeal arteries causes headache as far forward as the eye and as far back as the ear, depending on whether the stress is primarily on the more anterior or the more posterior branches. Dural, extradural or subdural tumors causing traction on these arteries in any part of their extent, from their origin at the foramen spinosum in the middle fossa to their terminal branches near the sagittal sinus, may thus cause headache.

c Traction on the large arteries at the base of the brain and their main cerebral branches or on the pia-arachnoid in immediate contact with them causes headache. When the traction is on the intracranial portion of the internal carotid arteries and the major components of the circle of Willis the headache occurs in the region of the eyes or in the front, top or sides of the head. Traction on the basilar and vertebral arteries and their branches produces headache in the back of the head and neck. Displacement of this entire arterial system from right to left causes a generalized headache, chiefly on the right, from the eye to the neck. Distention of the third ventricle causes traction on numerous arteries at the base of the brain and results in pain all over the head (fig. 17). Tumors in the region of the sella turcica or above it may cause pain by traction on the pain-sensitive arteries at the anterior end of the circle of Willis. The anterior cerebral artery, when under traction even as high as the genu of the corpus callosum, causes pain over or within the eye. Hence, tumors in the frontal lobe or in the corpus callosum causing traction on one or both of these arteries may produce pain in the region of the eye as described.

Since traction on pontile and internal auditory arteries causes pain within and behind the ear, tumors of the eighth nerve and others within the cerebellopontile angle or in the region of the internal auditory meatus may cause pain in the region about the ear.

d Distention and dilation of the intracranial and extracranial arteries results in headache (see introductory paragraph). The arteries responsible for such pain are pial arteries (chiefly at the base, as has been described), dural arteries (chiefly the middle meningeal), a few superficial branches of the internal carotid artery and many branches of the external carotid artery on the front, side and back of the head. Five varieties of headache may result from dilatation and distention of cranial arteries. (1) headache resulting from chemical agents, such as histaminic

or amyl nitrite,<sup>13</sup> (2) migraine headache,<sup>14</sup> (3) headache associated with fever or septicemia,<sup>15</sup> (4) headache associated with hypertension<sup>3a</sup> and (5) postconvulsive headache

e Inflammation involving the pain-sensitive structures at the base and the convexity of the brain causes severe headache. When inflammation is limited to the posterior fossa the headache is chiefly over the back of the head. When the inflammation is in the supratentorial fossa the headache is primarily frontal or vertical. The headaches associated with meningitis, subarachnoid hemorrhage or meningeal invasion by tumor are examples of headaches due to local tissue reaction or inflammation.

f Direct pressure by tumors on nerves possessing many pain-conducting fibers may cause pain. Thus, compression of the intracranial portion of the sensory division of the fifth cranial nerve results in pain in the front, top and side of the face and head. Similarly, compression of the intracranial portions of the ninth and tenth cranial nerves produces pain in and behind the corresponding ear, while compression of the upper cervical roots results in pain in the back of the head and neck.

Tumors probably do not commonly cause headache through circumscribed pressure on the dura even in the pain-sensitive areas. Thus, mere downward pressure on the dura of the floor of the anterior fossa, for example, does not cause headache. Although neoplastic invasion of the dura with the usual inflammatory reaction may be a cause of headache, as has been mentioned, traction and displacement of arterial and venous structures are the mechanical disturbances more likely to be responsible for headache in the presence of a tumor.

Because of its importance, the headache associated with increased intracranial pressure will be further considered. It is unlikely from the data given earlier that mere pressure, local or general, will of itself give rise to the incapacitating headaches that sometimes accompany this state. Other forces associated with the increase in pressure are more significant. Traction on the tributary veins which act as anchoring structures for the brain may be evaluated first.<sup>6b</sup>

It has been shown that stretching the many tributary veins which pass from the cerebral cortex to the dural sinuses produces pain. Also because of the arrangement and location of these vessels, they are pulled on not only when the brain is edematous or distended by dilated ventricles but when it sags as a result of sudden withdrawal of cerebrospinal or ventricular fluid. This was demonstrated by placing a balloon in one lateral ventricle. In this experiment both the dilatation and the sudden collapse of the walls of one lateral ventricle produced homolateral

13 Lake and others<sup>1a</sup> Hitz and Kammer<sup>1b</sup> Pickering and Hess<sup>2a</sup> Clark Hough and Wolff<sup>2b</sup>

14 Graham and Wolff<sup>5</sup> Sutherland and Wolff<sup>3a</sup>

15 Wolff<sup>1a</sup> Sutherland and Wolff<sup>3a</sup> Pickering<sup>3b</sup>

headache Under these circumstances distention or displacement of the third ventricle could be eliminated as a factor in production of the pain Moreover, it is unlikely that the procedure produced enough obstruction of cerebral arterial flow to increase the tension of the walls in the large arteries at the base

Second, headache occurring during increased intracranial pressure may result from traction on the large pial and cerebral arteries at the base of the brain and the proximal portions of their more immediate branches The pain associated with dilatation of the third ventricle is an example of such a mechanism in operation

Third, headache may result from traction on the middle meningeal artery, secondary to the stretch of the tightly drawn dura over the convexity of the cerebral hemispheres

Still another mechanism that deserves consideration is herniation of the cerebellum into the foramen magnum during increased intracranial pressure The protrusion of the tonsils and vermis of the cerebellum into the foramen magnum (during increased intracranial pressure) not only may put traction on the occipital sinus but may displace or stretch the upper cervical posterior roots This would result in occipital headache secondary to direct pressure on nerves possessing many pain-conducting fibers, that is, the sixth mechanism described in the foregoing paragraphs

Northfield,<sup>16</sup> in his explanation of headache from increased intracranial pressure due to ventricular block, parenchymal tumor or edema, advanced the view that headache "is due to some disturbance of the tension of the walls of the cerebral vessels and it is this disturbance of tension which provides the adequate stimulus for the excitation of pain" He compared the headache resulting from histamine with that resulting from increased intracranial pressure and assumed that in the case of both, dilatation of the pial arteries is responsible for the pain This argument is based in part on the observation made on animals that a gradual increase in intracranial pressure produces dilatation of the arteries and veins over the cerebral convexity<sup>16</sup> The mechanism of this vasodilatation has never been conclusively defined, but it is probably comparable to the cerebral vasodilatation associated with a slower blood flow following a fall in blood pressure or to the dilatation following inhalation of carbon dioxide<sup>17</sup> Vasodilatation of this magnitude may produce headache It is therefore conceivable that headache associated with increased intracranial pressure could in part originate in this manner It is probable, however, that such vasodilatation alone is less

16 Wolff, H G, and Forbes, H S The Cerebral Circulation V Observations of the Pial Circulation During Changes in Intracranial Pressure, *Arch Neurol & Psychiat.* **20** 1035 (Nov) 1928

17 Wolff, H G The Cerebral Circulation, *Physiol Rev* **16** 545, 1936

important as a mechanism for headache during increased intracranial pressure than is traction on pain-sensitive arteries and veins. Certainly these factors may combine.

Elsberg<sup>18</sup> suggested that "sudden changes in pressure conditions within the third ventricle and on the optic thalami that form its lateral walls may be a factor in some varieties of headache." The choroid plexuses, vessels and ependymal walls of the entire ventricular system have been demonstrated to be insensitive to various forms of direct stimulation, and, in addition, the thalamus has been pressed on through the floor of the lateral ventricle without producing pain. Therefore, whatever pain results from changes in intraventricular pressure probably is due to secondary stimulation of the more remote structures mentioned in the previous paragraphs.

3 *Headache and Referred Pain*—Referred pain is loosely defined as any pain which is felt at a site other than that of stimulation. Some prefer to limit the term to those distant pains that are accompanied by paresthesias and increased sensitivity of the skin at the site of reference. In this discussion referred pain will be used in the broader sense, to indicate pain both with and without increased sensitivity of the skin.

a *Headache and Referred Pain from Intracranial Structures* Because of the uniformity of response in the location of pain following stimulation of pain-sensitive intracranial structures, the following generalization is justified. Pain in front of a line drawn vertically from the ear indicates that a pain-sensitive structure of the superior surface of the tentorium (or above) is being stimulated, pain behind this line implies stimulation of a pain-sensitive structure beneath the tentorium.

It has been maintained that when referred pain is associated with "tenderness" of the skin, local infiltration of procaine hydrochloride not only decreases this local sensitivity but abolishes the referred pain.<sup>19</sup> The local sensitivity is decreased by infiltration with this anesthetic, but it has never been possible to eliminate headache or, indeed, to prevent the onset of the headache associated with pneumoencephalography or such agents as histamine by such infiltration.<sup>4</sup>

The following summary is a correlation of intracranial structures and the location of pain resulting from stimulation of these structures.

The structures which when stimulated give rise to pain in the general region of the eye and forehead are the dura of the anterior fossa, the anterior meningeal arteries, the structures innervated by the tentorial nerve (which include the superior surfaces of the tentorium, torcular Herophili, transverse and straight sinuses, the sagittal sinus in its posterior half and various tributary veins to these sinuses), the sylvian vein, the intracranial portion of the internal carotid artery, the vessels of the circle of Willis and the proximal portions of the larger cerebral branches, and the first division of the fifth nerve.

18 Weiss, S, and Davis, D. The Significance of Afferent Impulses from the Skin and the Mechanism of Visceral Pain, *Am J M Sc* **176** 517, 1928.

The structures which when stimulated give rise to pain felt in the temporal and parietal regions of the head are the middle meningeal arteries, the inferior cerebral veins of the temporal lobe that connect with the venous sinuses, and the anterior portion of the sagittal sinus and its venous tributaries. In the temporo-parietal region there is even more discrete localization, because stimulation of the more proximal parts of the midmeningeal arteries causes pain at a lower level than does stimulation of the more distal parts of these vessels.

When parietal pain is produced by stimulation of the midportion of the sagittal sinus and its tributaries it is localized near the vertex. Traction on the floor of a sella turcica containing a pituitary adenoma that had broken through the roof of the sphenoid sinus caused pain in the vertex. It was inferred that the mucous membrane of the sphenoid sinus and not the dura of the sella was the structure responsible for this pain.

The occipital and suboccipital regions of the head comprise even a smaller combined area than the frontoparietotemporal region, and localization of pain to any specific part of this posterior area is overprecise. Yet some structures in the posterior fossa are responsible for pain near the midline of the skull and in the upper cervical regions only, and other structures are responsible for pain in or behind the ear. The intracranial structures which when stimulated give rise to pain in or behind the ear are the undersurface of the walls of the torcular Herophili, the straight sinus and the transverse sinus, the walls of that half of the occipital sinus nearest the torcular, the wall of the sigmoid sinus and dura adjacent to it, the pontile and the internal auditory arteries, and the intracranial portions of the ninth and tenth cranial nerves. Stimulation at widely separated points along the transverse sinus results in separately localized pain within a comparatively small region on a line between the ear and the occipital protuberance.

The intracranial structures which when stimulated give rise to pain in the occiput (near the midline) and in the upper cervical region include the lower half of the occipital sinus and its branches at the margin of the foramen magnum, that part of the dura of the floor of the posterior fossa not covering or adjacent to the sigmoid sinus, the posterior meningeal arteries, the proximal portion of the posterior inferior cerebellar artery, the vertebral artery, the basilar artery, and the intracranial portions of the eleventh and possibly the twelfth cranial nerves.

Pain in the back of the head and neck without the more specific localizations mentioned results from stimulation of the posterior roots of the upper cervical nerves.

Persons with intracranial lesions which produce localized headache often have a perversion of sensation to superficial stimuli in that region.<sup>19</sup> The response to stimulation with cotton, pressure and pinprick in the region is in the nature of a paresthesia with hypersensitivity or hyperalgesia. Therefore, it is conceivable that an area of such perversion of sensation might help to fix the site of an intracranial disease process, be it a tumor, a hematoma, inflammation or a scar. In actual experience, it is found that the test is sometimes useful when dealing with lesions that are on or near the surface of the brain and impinge directly on pain-sensitive structures. Brief histories of 2 patients will serve as examples.

<sup>19</sup> Lewy, F. H. The Localization of Intracranial Lesions, *Ann Surg* **109** 28, 1939.

CASE 1—A 28 year old woman had the single complaint of persistent pain just behind the left ear for two years. On examination there were diminished corneal sensation on the left and slight incoordination of movements on the left side of the body. Pressure, touch and pinprick on the scalp in a localized region behind the left ear resulted in a paresthesia or in hyperalgesia. At operation a left acoustic neurinoma was found.

Since the observations on sensitivity to pain in the posterior fossa indicate that stimulation of the dura in the region of the cerebellopontile angle, the wall of the sigmoid sinus, the pontile artery and the internal auditory artery produces pain exclusively in the region just behind the ear, it is reasonable to conclude that some or all of these structures were irritated by the tumor, which gave little additional clue to its presence.

CASE 2—A 50 year old man was admitted to the hospital in stupor which had become deeper after a series of short, generalized convulsive seizures six hours before. An unreliable history disclosed only the complaint of moderate headache for the preceding few months. The meager collection of abnormalities detected on examination suggested a lesion of the left hemisphere, but pressure over the right parietal region of the head caused much greater discomfort than pressure elsewhere. Operative exposure revealed a parietal subdural hematoma on the right.

Observations on sensitivity to pain have indicated that the principal intracranial structures responsible for pain in the parietal region are the middle meningeal artery and the more anterior portion of the wall of the sagittal sinus with its venous tributaries. It is reasonable to conclude that in this case one or all of these structures were stimulated by the hematoma.

In brief, unilateral hyperalgesia localized in the parietal area may indicate the presence of a lesion in the region of the middle meningeal artery, and hyperalgesia localized in the postauricular region may indicate the presence of a lesion in the region of the internal auditory meatus. On the other hand, areas of local hyperalgesia can be relied on to indicate the location of the lesion only when the lesion produces direct stimulation of a pain-sensitive structure. Even then an area of hyperalgesia above the eye, for instance, would not help one distinguish between lesions as remotely separated as those on the dura of the floor of the anterior fossa or on the supratentorial wall of the torcular Herophili.

Subcortical cerebral tumors which produce headache and areas of paresthesia and hyperalgesia do so only by distant and indirect effects on pain-sensitive structures. Cerebellar tumors commonly produce, besides pain in the back of the head, pain and tenderness over the eyes. Some have attributed the frontal pain to pressure of the tumor on the tentorium, but our observations have shown that pressure on the undersurface of the tentorium, greater than would result from any tumor, is required to produce pain in the frontal region. A more cogent explanation for pain and hyperalgesia of the frontal region in cases of cerebellar tumor is



the tension on tributary veins of the supratentorial sinuses that would inevitably result from the hydrocephalus. The following case will serve to illustrate the point.

CASE 3—A 12 year old girl was admitted to the hospital. The complaints were of frontal, occipital and suboccipital headache and recurrent attacks of vomiting for seven months. There was hyperalgesia of the scalp just above the right eye and in both suboccipital regions, there were markedly choked disks and slight nystagmus but no other localizing signs of a tumor. A preoperative diagnosis of cerebellar tumor was made, and ventriculographic examination showed symmetric dilatation of the lateral and third ventricles, with the fluid under increased pressure. Operation disclosed a benign obstruction of the aqueduct of Sylvius.

In this instance the areas of headache and abnormal sensory perception in the scalp were definite and were similar to those encountered in patients with cerebellar tumors. The observations made at operation proved that the pain did not result from any local effects of the lesion but only from the indirect effects of hydrocephalus on many pain-sensitive structures in both the supratentorial and the infratentorial fossae.

Thus, it is evident that local tenderness of the scalp serves as an index to the structures responsible for pain but cannot be relied on implicitly to localize the lesion that initiates the stimulus, especially in the presence of hydrocephalus and generalized increase in intracranial pressure.

b Headache and Referred Pain from Extracranial Structures of the Head and Neck. Pain that has its origin in the extracranial structures of the head occurs mostly at or near the site of stimulation. Yet, if intense enough, the pain which arises in any structure of the head, such as the skin and arteries of the head and face,<sup>20</sup> the mucus membranes of the mouth, the eyes or the teeth, may spread to other parts of the head innervated by the same division or other divisions of the fifth cranial nerve. Similarly, intense pain arising in the neck from such structures as the skin, arteries<sup>20</sup> and muscles may spread from one cervical segment to the next and thus be felt over the occiput as high as the vertex. The special sites of reference of pain from the paranasal sinuses are under investigation.

c Headache and Referred Pain from Thoracic, Abdominal and Pelvic Viscera. Referred pain implies intimate anatomic connection between the site stimulated and the site at which pain is felt, even though these two regions are topographically widely separated. Headache as referred pain from intracranial structures and even from extracranial structures of the head and neck presents no difficulties, since pain is felt in that area on the surface which is supplied by the same nerve as the

<sup>20</sup> Fay <sup>25</sup> Sutherland and Wolff <sup>3a</sup>

structures stimulated Headache in association with dysfunction of other parts of the body, however, not only is more complicated but seldom is referred pain

In order to separate the headaches that actually are referred pain from those that are not, further consideration of the features which characterize referred pain is desirable First, referred pain and the associated paresthesia of the skin need not be diffused over all parts of that segment to which it is referred but may be experienced in a part of the dermatome Second, if the intensity of the afferent impulses from the stimulated site is great enough, the pain and paresthesia may spread from one segment to that immediately adjoining it, such spread may include the corresponding segments on the opposite side of the body Third, the spread of pain from one segment to another is progressive and orderly, so that intense pain may be experienced far from the segment in which it begins One may observe from the account of the progression or find at the time of examination that pain and perhaps paresthesia are still present in the intermediate segments even though the complaint is centered on the more remote segments

Headaches that are referred pain from sources other than the head do occur and have the aforementioned distinguishing features but are indeed rare Coronary occlusion is sometimes associated with such headaches The pain of coronary occlusion may begin over the precordium and spread to the fifth finger and in succession to the other fingers of the hand, up the neck to the angle of the jaw and back teeth and over the back of the head as high as the vertex

The extent of the spread of pain depends on the intensity of the pain, and the more intense the pain the greater is the spread The severe pain of gallbladder and renal colic, therefore, may sometimes spread to the head, but such headache is exceedingly rare

There is often confused with the limited variety of referred headache just described an entirely different category of headache, to be mentioned here only for clarification Thus, when thoracic, abdominal, pelvic or any systemic disease is associated with fever or sepsis, headache usually results It has been shown that headaches associated with these states are caused by dilatation of the cerebral arteries<sup>21</sup> and that the site of origin of the sepsis has no bearing on the degree or site of the vasodilatation or the location of the headache In the light of these new data it is relevant to consider the often cited instances of headache resulting from thoracic disease described by Head<sup>21</sup>

Head maintained that disease of the structures innervated by thoracic segments is commonly associated with headache of specific localization

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<sup>21</sup> Head H On Disturbance of Sensation, with Especial Reference to the Pain of Visceral Disease, *Brain* 17 339, 1894

He cited as evidence that disease of the tenth thoracic segment is associated with headache over the occiput, disease involving the eighth thoracic segment, with headache of the vertex, disease involving the seventh thoracic segment, with headache in the temporal region, and disease involving the sixth thoracic segment with headache over the eyes and temples. When the cases presented as evidence for his thesis are analyzed, it is seen that the patient with headache associated with disease of the tenth thoracic segment was suffering from bacterial endocarditis with lesions of the aortic and mitral valves. The patient with disease involving the eighth thoracic segment had pulmonary tuberculosis with fever. The patient with disease involving the seventh thoracic segment had a severe anemia and gastralgia. The patient with disease involving the sixth segment had rheumatic endocarditis with aortic stenosis.

The incidence of fever and sepsis in these patients is to be noted. The headache was constantly experienced by Head's patients in this or that portion of the head in connection with one or another thoracic segment, but this has not been noted with our patients. On the other hand, it was usual to find the headache predominantly in the temporal, parietal, vertical or occipital regions in different patients at different times.

#### SUMMARY AND CONCLUSIONS

The sensitivity to pain of the tissues covering the cranium, the cranium itself and most of the intracranial structures has been ascertained from a series of 30 patients<sup>7</sup> during surgical procedures on the head. Some of the "pain pathways" and the mechanisms of headache are defined.

The use of a variety of stimuli has resulted in the following conclusions about the sensitivity to pain of the structures investigated:

1. Of the tissues covering the cranium, all are more or less sensitive to pain, the arteries being especially so.

2. Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain are sensitive to pain.

3. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses, are not sensitive to pain.

With the exception of those sensations that resulted from stimulation of the parenchyma and nerves, the only sensation that was experienced on stimulation of the intracranial structures was pain.

Stimulation of the pain-sensitive intracranial structures on or above the superior surface of the tentorium cerebelli resulted in pain in various

regions in front of a line drawn vertically from the ears across the top of the head. The pathways for this pain are contained in the fifth cranial nerve.

Stimulation of the pain-sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and the upper three cervical nerves.

From the data available, six basic mechanisms of headache have been formulated. Headache may result from (1) traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses, (2) traction on the middle meningeal arteries, (3) traction on the large arteries at the base of the brain and their main branches, (4) distention and dilatation of intracranial and extracranial arteries, (5) inflammation in or about any of the pain-sensitive structures of the head, and (6) direct pressure by tumors on the cranial and cervical nerves containing many pain-afferent fibers from the head.

Intracranial diseases commonly cause headache through more than one of these mechanisms and by involvement of more than one pain-sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly responsible for headache.

Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain-sensitive structures. Since disease of remotely separated pain-sensitive structures may cause pain and hyperalgesia in identical areas, the clinical usefulness of such localization is limited. But unilateral hyperalgesia localized in the parietal area indicates the possibility of a lesion near the middle meningeal artery, and hyperalgesia localized to the postauricular region indicates the possibility of a lesion in the region of the internal auditory meatus.

Many of the anatomic drawings accompanying this paper are based on illustrations in the publication of Northfield<sup>61</sup> and in the following textbooks on anatomy: Toldt, C. *Anatomischer Atlas*, edited by F. Hochstetter, ed. 17, Berlin, Urban & Schwarzenberg, 1937; Morris, H. *Human Anatomy*, edited by C. M. Jackson, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923; Bourguery, J. M. *Traite complet, de l'anatomie de l'homme*, Paris, C. A. Delaunay, 1840; Spalteholz, K. W. *Hand Atlas of Human Anatomy*, translated from the seventh German edition by L. F. Barker, ed. 4, Philadelphia, J. B. Lippincott Company, 1923; Gray, H. *Anatomy of the Human Body*, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936; Sobotta, J. *Atlas of Human Anatomy*, edited from the sixth German edition of J. P. McMurrich, New York, G. E. Stechert & Company, 1930.

Miss Helen Goodell helped in the preparation of the manuscript and the drawings.

## DIRECT INGUINAL HERNIAS

A STUDY OF SIX HUNDRED AND FIVE HERNIAS AND OF FIVE  
HUNDRED AND SIXTY-FIVE REPAIRS

HAROLD J. SHELLEY, M.D.

FORT WORTH, TEXAS

This study covers 605 direct inguinal hernias, none of which had been operated on previously.<sup>1</sup> Included were all direct hernias in patients admitted to the wards at St. Luke's Hospital, New York, from 1926 to 1935 inclusive, and all repairs of direct inguinal hernias from 1916 to 1925 inclusive, subsequently observed for nine months or longer. Of the 605 hernias, 565 were repaired. Among the latter, 458 were followed for nine months or longer. Sixty-eight recurrences were discovered, giving a recurrence rate of 14.8 per cent. The average follow-up time was thirty-three and two-tenths months. The average time after operation at which the recurrences were discovered was twenty-six months.

These direct hernias comprised 13.6 per cent of all hernias and 16.6 per cent of all inguinal hernias included in the study as outlined in the foregoing paragraph.

### ETIOLOGIC FACTORS

*Onset (Age at Which Hernias Were First Noted)*—Only 2 per cent of these hernias were first noted during the first twenty years of life. Included in the five year period from the twentieth to the twenty-fifth year of life was the smallest percentage of hernias, 6.8 per cent, found in any five year group from 20 to 55 years of age. The percentages noted in the five year periods from 25 to 55 years were relatively equal. The highest incidences were in the fifth decade of life, both five year groups showing 15.9 per cent of the hernias in this entire group. From the fifty-fifth year on, each successive group showed a marked decrease in incidence. The average age of the patients when these direct inguinal hernias were first noted was 40.8 years. This is ten years later in life than was the case with incomplete indirect inguinal hernias.

The incidences of recurrence were fairly evenly spread over the five year periods from the age of 30 years on. When the patients were

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From the Surgical Services of St. Luke's Hospital.

<sup>1</sup> All figures in regard to incomplete and complete indirect inguinal hernias in this paper are from the following two papers published by me: *Incomplete Indirect Inguinal Hernias. A Study of 2,462 Hernias and 2,337 Repairs.* Arch. Surg. 41: 747-771 (Sept.) 1940. *Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs.* South. Surgeon 9: 257-268 (April) 1940.

under 25 years of age at the time these hernias were first noted, no recurrences were found following the repair. In patients between the ages of 20 and 40 years when the hernias were first noted the recurrence rate was 14.5 per cent, in patients 40 to 60 years old, 15.0 per cent, and in patients 60 to 80 years old, 23.8 per cent.

*Age at Time of Admission or Operation*—Few of these hernias (11 per cent) were repaired surgically in patients under 20 years of age. Only 3.5 per cent were repaired in patients between the ages of

TABLE 1—*Age at Which Hernia Was First Noted*

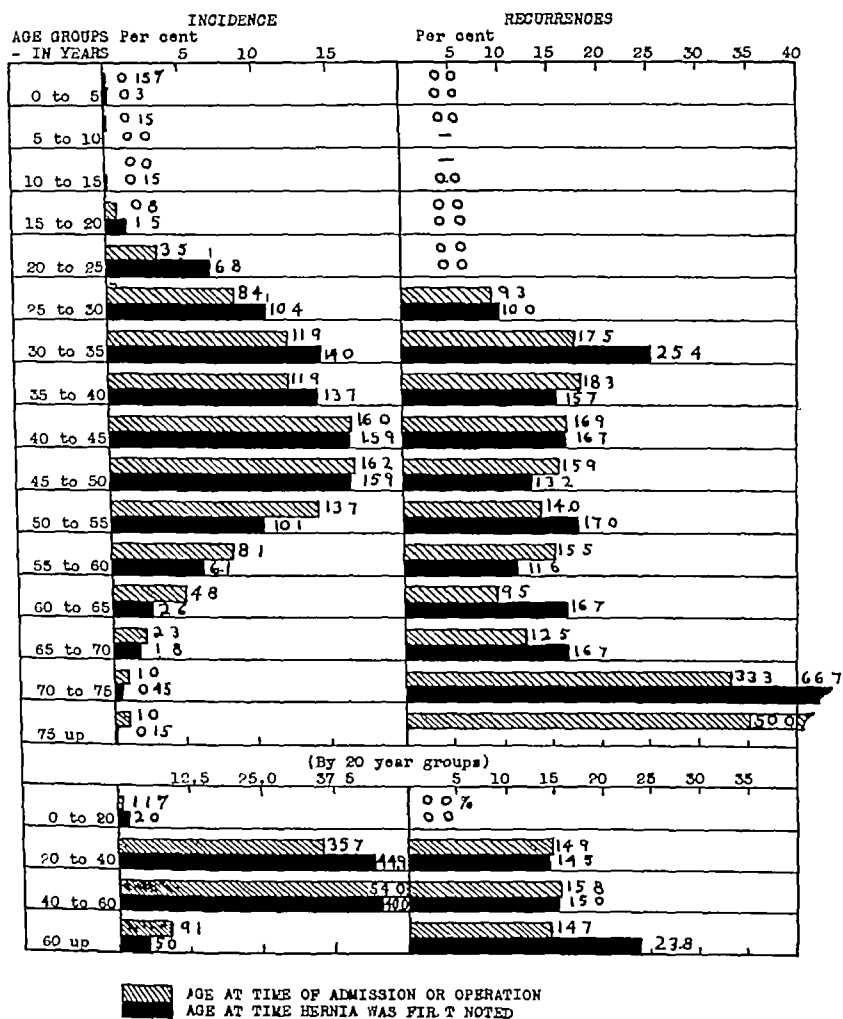
Age Group, Years	Total Hernias	Per Cent of Entire Group	Number Followed Postopera- tively	Number of Recur- rences	Per Cent Recurrences
0 to 5	2	0.3	2	0	0.0
5 to 10	0	0.0			
10 to 15	1	0.15	1	0	0.0
15 to 20	9	1.5	8	0	0.0
20 to 25	41	6.8	34	0	0.0
25 to 30	63	10.4	50	5	10.0
30 to 35	85	14.0	59	15	25.4
35 to 40	83	13.7	70	11	15.7
40 to 45	98	15.9	72	12	16.7
45 to 50	96	15.9	68	9	13.2
50 to 55	61	10.1	47	8	17.0
55 to 60	37	6.1	26	3	11.6
60 to 65	16	2.6	12	2	16.7
65 to 70	11	1.8	6	1	16.7
70 to 75	3	0.45	3	2	66.7
75 to 80	1	0.15	0		
Totals	605	100.0 100.0	458	68	14.8 14.8

The average age of the patients when direct inguinal hernias were first noted was 40.5 years.

20 and 25 years, and but 4.6 per cent in all before the twenty-fifth year of life. The age incidence at the time of admission to the hospital or operation increased up to the five year period from 45 to 50 years, with an incidence of 16.2 per cent. Each successive five year group following the fiftieth year of life showed a marked decrease. Throughout, greater percentages of patients were found in the more advanced age groups at the time of admission or operation as compared to the corresponding figures for incomplete indirect inguinal hernias, the average age for the former being 43.7 years and for the latter 34.8 years.

No recurrences were found following repairs of direct inguinal hernias performed on patients under the age of 25 years. The recur-

rence rate was 9.3 per cent for the age group 25 to 30 years. The incidences of recurrence were roughly the same in the various five year periods from 30 to 70 years. Beyond the latter age the numbers of followed repairs were too small to give significant recurrence rates.



Age incidence

The percentages of recurrence in the twenty year groups from the age of 20 years on were essentially the same for each group, varying only from 14.7 to 15.8 per cent. Apparently the age of the patients at the time their direct hernias were repaired had little effect on the expectation of recurrence.

*Sci* —A great majority of these hernias occurred in males, 96.9 per cent. This compared with 88.7 per cent of incomplete indirect inguinal hernias. Only 3.1 per cent were found in females, which is about

TABLE 2—*Age at Time of Admission or Operation*

Age Group, Years	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
0 to 5	1	0.15	1	0	0.0
5 to 10	1	0.15	1	0	0.0
10 to 15	0	0.0			
15 to 20	5	0.8	5	0	0.0
20 to 25	21	3.5	15	0	0.0
25 to 30	51	8.4	43	4	9.3
30 to 35	72	11.9	57	10	17.5
35 to 40	72	11.9	60	11	18.3
40 to 45	97	16.0	71	12	16.9
45 to 50	98	16.2	69	11	15.9
50 to 55	83	13.7	57	8	14.0
55 to 60	49	8.1	45	7	15.5
60 to 65	29	4.8	21	2	9.5
65 to 70	14	2.3	8	1	12.5
70 to 75	6	1.0	3	1	33.3
75 to 80	4	0.7	2	1	50.0
80 to 85	2	0.3	0		
Totals	605	100.0 100.0	458	68	14.8 14.8

The average age of the patients at the time of admission to the hospital or operation for direct inguinal hernias was 43.7 years.

TABLE 3—*Sex*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Male	586	96.9	440	67	15.2
Female	19	3.1	18	1	5.5
Totals	605	100.0	458	68	14.8

one fourth of the incidence of incomplete indirect inguinal hernias in females.

The recurrence rate for males, 15.2 per cent, was double that for females after repairs of incomplete indirect inguinal hernias. The recurrence rates for these two types of hernia in females were essentially the same for direct hernias 5.5 per cent and for incomplete indirect inguinal hernias 4.9 per cent.



*Race*—The division of these hernias according to the race of the patients was essentially the same as that found in the study of incomplete indirect inguinal hernias, as follows white patients, 94.7 per cent, Negroes, 5 per cent, and yellow patients, 0.15 per cent. These figures corresponded closely to the racial proportions among the general admissions to the hospital.

*Trauma*—A history of definite trauma as the etiologic factor in the development of their direct inguinal hernias was given by 31.4

TABLE 4—*Race*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
White	574	94.7	433	65	15.0
Negro	30	5.0	24	3	12.5
Yellow	1	0.15	1	0	0.0
Totals	605	100.0	458	68	14.8

TABLE 5—*History of Definite Trauma as Etiologic Factor\**

History of Trauma	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Absent	415	68.6	323	50	15.5
Positive*	190	31.4	136	18	13.2
Totals	605	100.0	458	68	14.8

\* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied a history of definite trauma as the etiologic factor in the development of their hernias was given by 26 per cent of the patients who first noted their hernias after the age of 15 years (Shelley, H. J. Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs, South Surgeon 9: 267-268, 1930).

per cent of the patients, as compared to 26.7 per cent of the patients with incomplete indirect inguinal hernias (see note under table 5).

The proportionate decrease in the incidence of recurrence among patients giving a history of trauma as the etiologic factor was not as definite as with incomplete indirect inguinal hernias. With no history of trauma, the incidence of recurrences was 15.5 per cent, as compared to 13.2 per cent when such a history was given.

#### SYMPTOMS

*Pain*—A slightly greater percentage of these patients gave a history of pain associated with their direct inguinal hernias than was noted with incomplete indirect inguinal hernias (52.2 per cent of the former and 49.7 per cent of the latter).

*Duration*—The average elapsed time from discovery of these hernias to the patient's admission to the hospital or repair was one year less than the corresponding figure for incomplete indirect inguinal hernias. The average duration, as defined in a foregoing section, was two and nine-tenth years for the former as compared to three and nine-tenths years for the latter.

The length of time for which the patients had had their direct inguinal hernias before operative repair apparently had little effect, if any, on the recurrence rate.

TABLE 6—*History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	289	47.8
Positive	316	52.2
Total	605	100.0

TABLE 7—*Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
To 1 week	74	12.2	60	8	13.3
To 1 month	143	23.6	110	16	14.5
First 6 months	270	44.6	204	30	14.7
Second 6 months	65	10.7	57	9	15.8
To 1 year	335	55.4	261	39	14.9
0 to 5 years	463	76.5	363	59	16.3
5 to 10 years	74	12.2	40	4	8.2
0 to 10 years	537	88.8	412	63	15.3
10 to 20 years	47	7.8	31	4	12.9
20 to 30 years	20	3.3	14	1	7.1
30 to 40 years	1	0.15	1	0	0.0
Totals	605	100.0	458	68	14.8

The average duration (time elapsed from discovery to time of admission or operation) for direct inguinal hernias was 2.9 years.

#### PHYSICAL FINDINGS

*Size*—As compared to the findings with incomplete indirect inguinal hernias, the incidence of direct inguinal hernias with the sac of such a size that it was contained entirely in the inguinal canal was one fourth greater, 32.6 per cent for direct hernias and 26.7 per cent for incomplete indirect hernias. The percentage of hernias which extended beyond the external ring but not into the scrotum was slightly more than one third greater in the case of direct hernias, 55 per cent compared to 40.7 per cent. In contrast to these increases in incidence, scrotal hernias

showed an incidence of only slightly more than one third that found with incomplete indirect inguinal hernias, 12.4 per cent compared to 32.6 per cent

The incidences of recurrence for the two groups in which the sac extended just beyond the external ring or into the scrotum were more

TABLE 8—Size

Size of Hernia †	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	197	32.6	146	13	8.2	0 in 106 operations	0.0
Size II	333	55.0	259	45	17.4	1 in 163 operations	0.6
Size III	75	12.4	63	11	20.9	1 in 43 operations*	2.3
Totals	605	100.0	468	68	14.8	1 in 312 operations*	0.32

\* The single death was due to a volvulus which developed after operative reduction and repair of a strangulated hernia. The strangulation developed in an old incarcerated hernia.

† Size I Hernias in which the sac was limited in extent to the inguinal canal.

Size II Hernias in which the sac extended beyond the external ring but not into the scrotum.

Size III Hernias in which the sac extended into the scrotum.

TABLE 9—Unilateral and Bilateral Hernias\*

	(A) Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Unilateral right	149	24.7	113	15	13.3
Unilateral, left	98	16.2	78	12	15.4
Total unilateral	248	40.9	191	27	14.1
Total bilateral	357	59.1	267	41	15.4
Total right	328	54.2	251	40	15.9
Total left	277	45.8	207	28	13.5
Totals	605	100.0	458	68	14.8

(B)

Bilateral hernias repaired separately recurrences 15.2%

Bilateral hernias repaired at one sitting recurrences 15.6%

(C)

Unilateral hernias recurrences right 55.6% of total left 44.5% of total

Bilateral hernias recurrences right 61.0% of total left 39.0% of total

\* Each hernia was counted individually. Each direct inguinal hernia was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

than twice that found when the sac was limited to the inguinal canal, 17.4 and 20.9 per cent for the former and 8.2 per cent for the latter.

The only death following repair of a direct inguinal hernia occurred in the group in which the sac extended into the scrotum, giving a mortality rate for that group of 2.3 per cent. This death followed operative reduction and repair of a strangulated hernia.

*Unilateral and Bilateral Hernias*—The incidence of bilateral hernias among direct inguinal hernias was nearly twice that found among incom-

*Type 1A*—Same as type 1, except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur

*Type 2*—Repair with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle, after the technic of Bassini, with catgut sutures only

*Type 2A*—Same as type 2, except that the conjoined tendon was sutured to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle, after the technic of McArthur

*Type 2B*—Same as type 2, except that a fascial suture from the fascia lata was used to suture the conjoined tendon to the inguinal ligament, after the technic of Gallie

*Type 3*—Repair with transplantation of the cord between the overlapped layers of the external oblique aponeurosis, after the technic of Willy-Andrews, with catgut sutures only

*Type 4*—Repair with transplantation of the cord external to the external oblique aponeurosis, with or without overlapping of the aponeurosis, after the technic of Halsted, with catgut suture material only

*Type 4A*—Same as type 4, with a fascial suture from the aponeurosis of the external oblique muscle used to suture the conjoined tendon to the inguinal ligament, after the technic of McArthur

*Type 4B*—Same as type 4, with a fascial suture obtained from the fascia lata used to suture the conjoined tendon to the inguinal ligament, after the technic of Gallie

*Type 5*—Any of the aforementioned types of repair in which the rectus muscle or the anterior sheath of the rectus muscle was sutured to the inguinal ligament. This included no repairs in which fascial sutures were utilized

In a consideration of the results obtained with the various types of repair, one must bear in mind that the majority of those hernias which presented particular difficulties as to obtaining a permanent cure fell in the classifications in which a fascial suture was used or transplantation of the rectus muscle or sheath was done. Also, the majority of those hernias which presented the greatest probability of permanent cure were repaired with a technic in which the cord was not transplanted

Suture of the rectus muscle or of the anterior sheath of the rectus muscle to the inguinal ligament in the repair of direct inguinal hernias proved to give disappointing results, as had also been observed in repairs of incomplete indirect inguinal hernias. The use of this technic was followed by recurrence in one fourth of the repairs. Its use

has been discontinued. The recurrence rate of 11.9 per cent, which is the average for all repairs excluding those in which transplantation of the rectus muscle was done, represents a much fairer expectation of recurrence in the repair of direct inguinal hernias as done at present than does the figure 14.8 per cent, which was the recurrence rate for the entire group.

Again, as with repairs of incomplete indirect inguinal hernias, transplantation of the cord superficial to the aponeurosis of the external oblique muscle without use of a fascial suture gave the highest recurrence rate, 16.9 per cent, except in that group in which transplantation of the rectus muscle was done.

Also, the average recurrence rate when fascial sutures were used, 10.4 per cent, was less than that noted when they were not used, 17.1 per cent. Even after elimination of those repairs in which transplantation of the rectus muscle or sheath was done, the recurrence rate, 13 per cent, was greater than when fascial sutures were used, 10.4 per cent. As has been stated previously, the latter group contained a much greater proportion of hernias in which attainment of a satisfactory repair presented the greater difficulties. Consequently, the expectancy recurrence in the group repaired with fascial sutures would have been correspondingly larger had the two groups of hernias been repaired by the same method.

The incidence of wound infection, 4.2 per cent, was one third more than in incomplete indirect inguinal repairs. This increase was associated with practically all types of operation but appeared to have little influence on the recurrence rates.

#### POSTOPERATIVE COMPLICATIONS

The incidence of postoperative complications, 21.1 per cent, was double that following repair of incomplete indirect inguinal hernias, 10.4 per cent. An increase would be normally expected, as repair of direct inguinal hernias requires a more extensive operation on the average. This increase was also present with respiratory complications, the figures being 13.3 and 7.3 per cent respectively. The incidences of circulatory complications were essentially the same, 3 per cent for direct inguinal hernias and 2.8 per cent for incomplete indirect inguinal hernias. The former type of complication gave an increase in the recurrence rate to 21 per cent, while the latter gave essentially the average, the figure being 14.3 per cent.

Wound infection developed after 4.2 per cent of the repairs as compared to 3.5 per cent of repairs of incomplete indirect inguinal hernias. Recurrences were found later with 16.3 per cent of the infected wounds, as compared to 14.8 per cent for the entire group of repairs of direct inguinal hernias.

## OPERATIVE MORTALITY

Only 1 death followed the 312 successive repairs of direct inguinal hernias performed in the ten year period from 1926 to 1935 The mor-

TABLE 12—*Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post operative Stay in Hospital, Days	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	39	7.9	19.0	36	9	25.0	5.1	0	0.0
2 Wound infection	24	4.2	20.1	19	3	16.3		0	0.0
3 Bronchopneumonia	16	2.8	32.0	11	1	9.1	0.0	0	0.0
4 Lobar pneumonia	9	1.6	46.1	8	1	12.5	22.2	0	0.0
5 Hematomata	7	1.2	15.0	7	1	14.3	0.0	0	0.0
6 Cystitis	4	0.7	21.0	3	2	66.7	0.0	0	0.0
7 Deep phlebitis	4	0.7	31.0	3	0	0.0	0.0	0	0.0
8 Pulmonary embolus	4	0.7	30.8	3	1	33.3	0.0	0	0.0
9 Acute tonsillitis	3	0.5	20.0	1	0	0.0	0.0	0	0.0
10 Hemorrhage—patient reoperated on	2	0.3	22.5	1	0	0.0	50.0	0	0.0
11 Pulmonary atelectasis	2	0.3	16.0	2	0	0.0	0.0	0	0.0
A Atelectasis (right lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
B Atelectasis (left lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
12 Pleurisy with effusion	1	0.2	28.0	0			0.0	0	0.0
13 Empyema	1	0.2	103.0	1	1	100.0	0.0	0	0.0
14 Urethritis	1	0.2	14.0	1	0	0.0	0.0	0	0.0
15 Uremia	1	0.2	39.0	1	0	0.0	100.0	0	0.0
16 Volvulus	1	0.2	7.0	0			0.0	1	100.0
Totals	119	21.1		97	19	19.6	5.0*	1	0.84

\* Excluding those patients whose only complication was wound infection

TABLE 13—*Postoperative Respiratory Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post operative Stay in Hospital, Days	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	39	7.1	19.0	36	9	25.0	5.1	0	0.0
2 Bronchopneumonia	16	2.8	32.0	11	1	9.1	0.0	0	0.0
3 Lobar pneumonia	9	1.6	46.1	8	1	12.5	22.2	0	0.0
4 Pulmonary embolus	4	0.7	30.8	3	1	33.3	0.0	0	0.0
5 Acute tonsillitis	3	0.5	20.0	1	0	0.0	0.0	0	0.0
6 Pulmonary atelectasis	2	0.3	16.0	2	0	0.0	0.0	0	0.0
A Atelectasis (right lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
B Atelectasis (left lung)	1	0.2	16.0	1	0	0.0	0.0	0	0.0
7 Pleurisy with effusion	1	0.2	28.0	0			0.0	0	0.0
8 Empyema	1	0.2	103.0	1	0	0.0	0.0	0	0.0
Total	75	13.3		62	13	21.0	5.3	0	0.0

ality figure was 0.32 per cent. The patient who died was 75 years of age. Strangulation had developed in an old incarcerated hernia, the strangulation having been present two days before the patient's admis-

sion to the hospital. Resection of the strangulated loop of ileum was not considered necessary. Death occurred on the seventh postoperative day, immediately following an operation for volvulus.

## FOLLOW-UP DATA

Of the 605 direct inguinal hernias studied, 40 were not repaired. Of the 565 patients with hernias repaired, 41 did not return for follow-up observation. Sixty-six were examined over periods of less than nine months without discovery of a recurrence. Among 524 repairs

TABLE 14—*Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post operative Stay in Hospital Days	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Hematomas	7	1.2	15.0	7	1	14.3	0.0	0	0.0
2 Deep phlebitis	4	0.7	31.0	3	0	0.0	0.0	0	0.0
3 Pulmonary embolus	4	0.7	30.8	3	1	33.3	0.0	0	0.0
4 Hemorrhage—patient reoperated on	2	0.3	22.5	1	0	0.0	50.0	0	0.0
Totals	17	3.0		14	2	14.8	6.5	0	0.0

TABLE 15—*Deaths (1926-1935)*

Operative Deaths*	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death	Cause of Death
1	75	Yes	2 days	No	7 days after operation	Volvulus

\* One death in 312 operations giving a mortality rate of 0.32 per cent.

examined at some time after the patient left the hospital (average time of follow-up, twenty-nine and five-tenths months), 68 recurrences were discovered, giving a recurrence rate of 12 per cent.

Among the 458 repairs followed for nine months or longer or until a recurrence was discovered, the recurrence rate was 14.8 per cent. The average time of follow-up for this group (i.e., those followed for nine months or longer) was thirty-three and two-tenths months. The average time at which the recurrences were discovered was twenty-six months after the operation.

The number of follow-ups ending in successive periods with recurrences discovered in the corresponding periods are given in table 16 (B). Sixty-nine per cent of the total number of recurrences were found within

two years after the repairs were done. Nearly one third of the recurrences were discovered two years or more postoperatively, and one fourth, three or more years after the repairs were done.

The proportion of direct recurrences, 91.2 per cent, was greater than that which followed primary repair of incomplete indirect inguinal hernias, 60 per cent, although the former figure was the same as that which followed repair of indirect inguinal recurrences.

TABLE 16—*Follow-up Data*

A

Total number of hernias studied	605
Total with no operation	40
Total operations	565
Total operative deaths	1
Total with no follow up examination	41
Total with follow up under 9 months—no recurrences	66
Total with follow up 9 months and over (including recurrences)	458
Average follow up time for all cases followed 9 months and over	33.2 months
Total recurrences	68
Average postoperative time recurrences were first noted	26.0 months
Percentage of recurrences with follow up of 9 months and over	14.8%
Total number of operations examined postoperatively	524
Average follow up time (all followed cases)	29.5 months
Total recurrences	68
Percentage of recurrences (all followed cases)	12.0%
Recurrences indirect, 8.8%, direct, 91.2%	

B

Length of Follow Up*	Total Operations Followed	Per Cent of All Followed Operations	Total Recurrences Discovered	Percentage of Total Recurrences	Recurrence Percentage for Group
Under 9 months	86	16.4	20	29.4	23.2
9 months to 1 year	68	13.0	10	14.7	17.2
Under 1 year	154	29.4	30	44.1	19.0
1 to 2 years	145	27.7	17	25.0	11.7
2 to 3 years†	126	24.0	4	5.9	3.2
3 to 5 years‡	29	5.5	5	7.4	18.0
5 to 10 years	34	6.5	8	11.8	15.2
10 to 15 years	30	5.7	4	5.9	13.3
15 to 22 years	6	1.1	0	0.0	0.0
Totals	524	100.0	68	100.0	12.0

\* Cases included in that group in which the follow up period was ended either by failure to return again for examination or by discovery of a recurrence.

† Nearly one third of the recurrences were discovered 2 years or longer after the operation.

‡ One fourth of the recurrences were discovered 3 or more years after the operation.

## COMMENT

A study has been made of 605 direct inguinal hernias, of which 565 were repaired.

In a consideration of the recurrence rates given in the various tables for repairs of inguinal hernias, it must be borne in mind that division of these hernias into indirect and direct as a clearcut grouping is not possible.

All hernias which were indirect but showed a direct weakness or bulge were classified among the indirect inguinal hernias. All hernias



in which there was both indirect and direct herniation in the same inguinal canal were classified as indirect or direct, depending on which of the two sacs was the larger. This routine was carried out whether the sac was of the saddle bag variety or there were two internal openings placed some distance apart. All hernias in the semilunar line were considered as direct inguinal hernias, without differentiation.

As a result of this method of classifying the hernias, a considerable group fell within the classification of indirect hernias in which the direct weakness, bulge or smaller hernia was undoubtedly of much greater significance in the question of the probability of recurrence than was the larger, indirect sac which had caused the patient's decision to have the repair performed. Classifying the simpler direct types with these direct hernias would have lowered the incidence of recurrence for repair of direct hernias.

The average age at which these hernias were first noted was ten years later in life than the corresponding figure for incomplete indirect inguinal hernias. The average age at the time of admission or repair was nine years later in life than was the case with incomplete indirect inguinal hernias. The average duration of these hernias (from the time when they were first noted to the time of admission to the hospital or operation) was one year less than that of incomplete indirect inguinal hernias. The recurrence rate for direct hernias in males was double that for incomplete indirect inguinal hernias (15.2 and 7.5 per cent respectively), while for females these figures were nearly the same, 5.5 and 4.9 per cent respectively.

A history of definite trauma as the etiologic factor in the development of the direct inguinal hernias was given in a slightly greater proportion of cases than was the case with incomplete indirect inguinal hernias.

Fewer of the sacs of direct inguinal hernias extended into the scrotum than was found to be the case with incomplete indirect inguinal hernias. Correspondingly, a greater proportion extended only beyond the external ring or were limited to the inguinal canal. Repairs of direct inguinal hernias with the longer sacs were followed by greater increases in the percentages of recurrence than was found to be the case when the sac was limited to the inguinal canal.

A smaller percentage of direct hernias were incarcerated than was the case with indirect hernias although the percentages of strangulated hernias were practically the same in the two instances.

Repair of direct inguinal hernias by suture of the rectus muscle or the anterior sheath of the rectus muscle to the inguinal ligament was found to be an unsatisfactory procedure. Even after elimination of the aforementioned type of repair from all operations in which catgut sutures only were used a greater incidence of recurrence was found than that

which followed the use of fascial sutures. This was true notwithstanding the fact that a greater percentage of the more difficult repairs were included in the latter group. The conclusion may be drawn from this that use of a fascial suture in the repair of direct inguinal hernias is a worth while procedure.

Postoperative complications developed after twice as great a percentage of repairs of direct as of incomplete indirect inguinal hernias.

The incidence of direct and that of incomplete indirect inguinal hernias as to location (right or left) was the same.

Nearly twice as great a proportion of direct inguinal hernias as of incomplete indirect inguinal hernias were bilateral (i. e., were associated with an inguinal hernia of some type on the opposite side).

The proportion of direct recurrences following repair of direct inguinal hernias was the same as that following repair of indirect inguinal recurrences and 50 per cent greater than that following repairs of incomplete indirect inguinal hernias.

#### REPAIR OF DIRECT INGUINAL HERNIAS

As is the case with all other types of hernia, these repairs deserve careful, clean dissection, sutures should be tied only tight enough to give approximation of tissues, and perfect hemostasis must be obtained, the bleeding vessels being clamped and tied without inclusion of adjacent tissues. Approximation of the cut edges of the external oblique aponeurosis will be facilitated by placing the first suture at the medial end of the incision to form the external ring and drawing the cord downward, so that it lies in a straight line in the inguinal canal before this first suture is tied. If silk suture material is to be used, and I feel that it should be, no continuous sutures should be used. In closing the wound, particular care should be exercised to leave no dead spaces. This together with careful hemostasis, will prevent collection of serum in the closed incision.

The figures in this study would indicate that all, or practically all, direct hernias should be repaired by proper and careful use of a fascial suture. In my opinion, this should be done with a silk technic throughout. Whether part or all of the repairs should be done with a silk technic without fascial sutures, only a longer experience and a larger follow-up series for comparison than is now available at St. Luke's Hospital will determine.

It is my opinion that conversion of the direct sac into an indirect one in dissection of these hernias is a distinct improvement over isolation of the sac through the transversalis fascia at the point where it extends into the inguinal canal.

# USE OF SERIAL DILUTIONS IN DETERMINATION OF PROTHROMBIN BY THE ONE STAGE TECHNIC

J GARROTT ALLEN, M D

ORMAND C JULIAN, M D

AND

LESTER R. DRAGSTEDT, M D

CHICAGO

Recent advances in the study of blood coagulation have been stimulated by the discovery of vitamin K and its relation to prothrombin. While there is considerable variance of opinion as to the nature of blood coagulation, it can be assumed that at least five factors are necessary before this phenomenon occurs. These include ionizable calcium, thromboplastin, prothrombin, thrombin and fibrinogen. It is generally agreed that these substances act in the following manner, as was suggested by Howell<sup>1</sup> in 1914:

Based on this theory of coagulation, several methods for the measurement of prothrombin have been devised. Of these, the two stage method of Warner, Brinkhous and Smith<sup>2</sup> and the one stage method of Quick<sup>3</sup> have been more frequently employed than the others.

The two stage technic of Warner, Brinkhous and Smith is carried out as follows. Oxalated plasma is defibrinated by the addition of purified thrombin<sup>3</sup>. This defibrinated plasma is then incubated for thirty minutes to allow any residual thrombin to be inactivated by antithrombin. This plasma is then diluted serially and incubated with calcium chloride, thromboplastin and acacia, after which fibrinogen is added and the clotting time is recorded. The results are then calculated in terms of unitary prothrombin. By this method the clotting time is considered as the time necessary for fibrinogen to be converted into fibrin by thrombin.

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From the Department of Surgery of the University of Chicago

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1 Howell, W H. Theories of Blood Coagulation, *Physiol Rev* **15** 435-470, 1935

(a) Thromboplastin + prothrombin +  $\text{Ca}^{++}$   $\rightarrow$  thrombin

(b) Thrombin + fibrinogen  $\rightarrow$  fibrin

2 Warner, E D, Brinkhous, K. M, and Smith, H P. Quantitative Study of Blood Clotting, *Am. J. Physiol* **114** 667-675, 1936

3 Quick, A J, Stanley-Brown, M, and Bancroft, F W. A Study of the Coagulation Defect in Hemophilia and in Jaundice, *Am J M Sc* **190** 501, 1935

The one stage method developed by Quick is a measurement of the time necessary for prothrombin to be converted into thrombin and for the subsequent conversion of fibrinogen into fibrin by this thrombin. The technic itself is concerned with the addition of thromboplastin and calcium chloride to oxalated plasma, after which the clotting time is measured. The results are expressed in terms of a standard time of twelve to fifteen seconds.

By and large, the clinical results of these two methods have compared favorably. Theoretically, any difference between the two rests on the consideration of whether prothrombin is converted into thrombin instantaneously, as has been maintained by Quick, or whether this process is gradual and time consuming, as has been held by Smith. In practice the two stage method is more difficult to perform, and consequently the one stage method is more easily adapted to extensive clinical use. The thromboplastic substances employed by these workers are derived from different tissues, cephalin, as used by Quick,<sup>3</sup> is obtained from the rabbit brain, while the aqueous soluble tissue extract used by Smith<sup>2</sup> is obtained from beef lung. Smith and his associates<sup>4</sup> suggested that the tissue extract is more advantageous because of its water solubility, while cephalin as used by Quick represents an emulsion. We have found the lung extract very serviceable, and it remains potent for many weeks. The activity of crude thromboplastic substances may vary slightly from day to day, thus producing minor changes in the clotting times of both normal and abnormal plasmas. Consequently, it is more desirable to compare the clotting time of abnormal plasma with that of normal plasma in a test run at the same time than to compare the abnormal clotting time with a fixed standard coagulation time.

Experimental data are presented here concerning the determination of prothrombin by a modified one stage technic. All determinations were carried out at 37 C, with lung extract<sup>2</sup> as the thromboplastic substance and with a test of normal human plasma run with each group of determinations. Clotting times were determined on ten serial dilutions of each plasma, with concentrations ranging from 50 per cent to 5 per cent of the original undiluted plasma. A final standard volume was maintained with oxalated saline solution<sup>2</sup> in each sample. All volumetric measurements were made with micropipets.

In chart 1 is shown the clotting time of oxalated plasmas when serially diluted with oxalated saline solution, with addition of thromboplastin and calcium chloride. Curve 1 is representative of normal human plasma, while curves 2 and 3 represent prothrombin-deficient plasmas. It will be seen from this chart that it was necessary to dilute

<sup>4</sup> Smith H. P., Warner, E. D., and Brinkhous, K. M. Lung Extract and Ficed Coagulation, *Am. J. Physiol.* **107** 63-69, 1934.

the normal plasma to less than 35 per cent of its original concentration before any change in clotting time occurred. It is apparent from curves 2 and 3 that a prolonged clotting time may be evident in the 50 per cent plasma concentration or that it may appear at any point down to the 35 per cent level, according to the degree of prothrombin deficiency present. We have not observed an abnormal plasma which did not exhibit a prolonged clotting time before the 35 per cent plasma concentration was reached, although the degree of abnormality was sometimes so slight as to be difficult to read. In such cases the more dilute plasmas magnify any differences, so that they become more readily

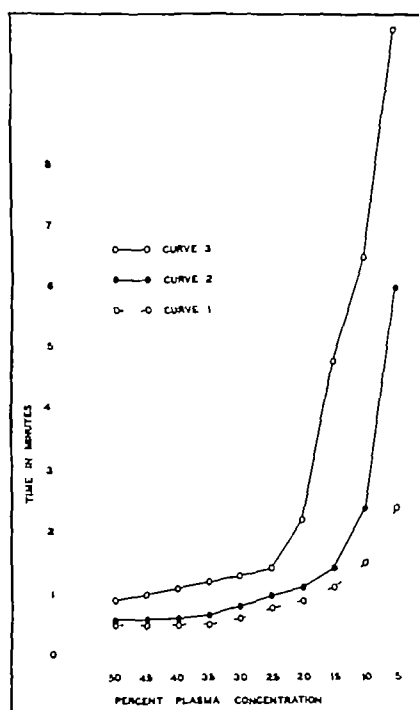


Chart 1—Relation between coagulation time and concentration of normal and of prothrombin-deficient plasmas

apparent. The results so obtained then can be compared with the clotting curve of the normal control. The early, straight line portion of the curve for normal plasma is probably representative of an excess of plasma prothrombin which this technic is not sufficiently sensitive to record.

When fibrinogen<sup>2</sup> was added in increasing volumes, thus replacing the ovalated saline solution used in maintaining the standard volumes of the serial dilutions, no significant deviation from the control clotting

time was observed until the 15 per cent plasma concentration was reached (chart 2). Since a small amount of prothrombin could still be demonstrated in the fibrinogen used, it appears that most, if not all, of this slight reduction in the clotting time could be accounted for on the basis of the prothrombin contained in this fibrinogen. From this curve it is highly suggestive that the dilution of fibrinogen which accompanies the dilution of prothrombin in the technic used here is not a factor in the alteration of clotting time.

The advantages of serial dilution in the one stage technic are readily apparent in cases in which the prothrombin response to vitamin K is minimal or sluggish. The case of nontropical sprue mentioned in the table illustrates such a sluggish response, sixteen days of oral administration of 2-methyl-1, 4-naphthoquinone were necessary to restore the prothrombin time to normal. The clotting times presented here have been interpreted in terms of the coagulation time of a single normal

*Slow Return to Normal of the Clotting Time in a Case of Nontropical Sprue*

No. of Days of Naphthoquinone Therapy	Per Cent of Plasma Concentration									
	50 Min	45 Min	40 Min	35 Min	30 Min	25 Min	20 Min	15 Min	10 Min	5 Min
1	0.83	0.90	1.01	1.10	1.19	1.30	2.10	4.70	6.40	10.00
5	0.80	0.89	0.97	1.08	1.30	1.42	1.60	1.82	3.25	7.00
7	0.65	0.65	0.65	0.76	1.00	1.24	1.30	1.60	2.80	6.50
11	0.52	0.55	0.57	0.61	0.71	0.85	0.90	1.14	1.64	4.40
16	0.46	0.46	0.46	0.46	0.57	0.72	0.80	0.95	1.46	3.40
Normal control	0.46	0.46	0.46	0.46	0.57	0.72	0.78	0.97	1.43	3.35

control. Thus it is seen that the more dilute plasmas more readily reflect minor changes in the clotting time.

In the course of these studies several patients showed prolongation of the clotting time of the more concentrated plasmas in the coagulation curve, while at the same time in the more dilute plasmas of these patients the clotting times approximated those of the normal control. An example of this phenomenon is shown graphically in chart 3. These data were obtained from the plasma of a patient during the course of serum sickness which appeared ten days after antipneumococcic rabbit serum had been given. At the height of the illness many spontaneous ecchymotic areas appeared in the skin and subcutaneous tissues. Whether this phenomenon represented release into the blood stream of an inhibitory, or heparin-like, substance is, of course, not known. It is interesting, however, that in the experimental animal Jaques and Waters<sup>5</sup> have recently

<sup>5</sup> Jaques, L. B., and Waters, E. T. The Isolation of Crystalline Heparin from the Blood of Dogs in Anaphylactic Shock, read at the meeting of the American Physiological Society, New Orleans, March 13-16, 1940, *Proc. Am. Physiol. Soc.*, 1940, p. 93.

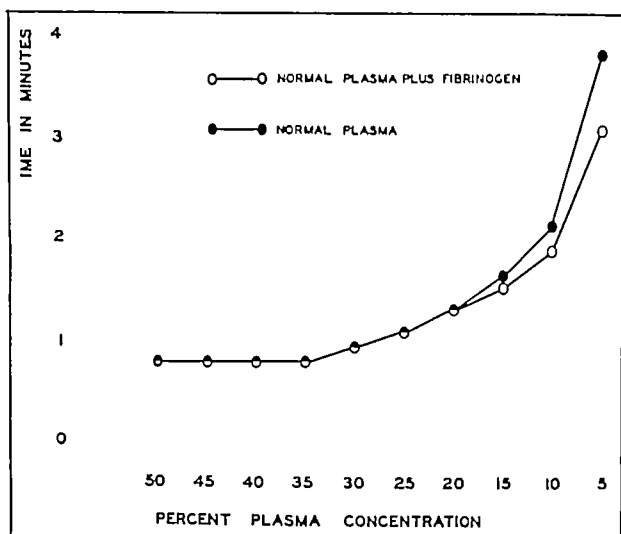


Chart 2—Graph showing that the dilution of fibrinogen accompanying the serial dilution of plasmas as employed in this study does not materially alter the coagulation curve

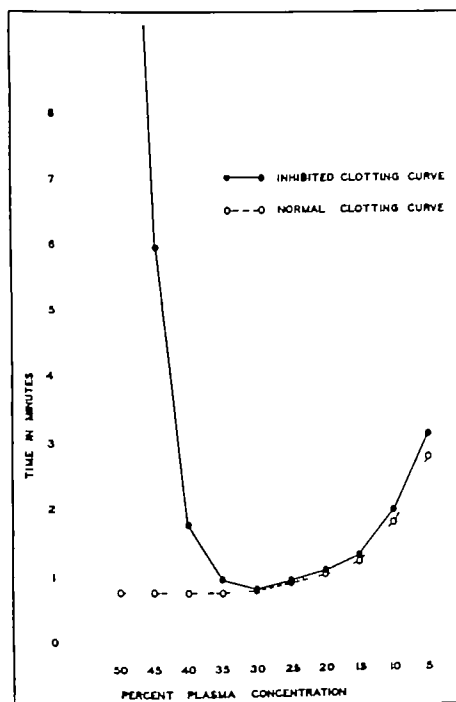


Chart 3—Inhibition of coagulation in a patient with serum sickness (see text)

reported the presence of crystalline heparin in the circulating blood after anaphylactic shock. Consequently, the data presented here are suggestive that a similar condition may occur in the human patient. The effect of an inhibitory substance was also demonstrated to a lesser degree in 4 patients during early postoperative periods. In none of these patients could this effect be demonstrated for more than forty-eight hours after its initial appearance. In vitro studies (not reported here) concerned with the addition of heparin to normal human plasma indicate that this anticoagulant is capable of altering the coagulation curve so that it has the same form as that shown in chart 3.

#### SUMMARY

A modification of the one stage technic for prothrombin determination is presented.

Variations of concentrations of fibrinogen in the plasma and its effect on prothrombin time are noted.

The value of serial dilutions of plasma in cases in which the response to vitamin K is sluggish is pointed out.

An inhibitory substance has been demonstrated in a patient suffering from serum sickness. The importance of employing the serial dilution technic for detection of this substance is discussed.

NOTE —Since submitting this paper for publication we have become aware of a report by Kark and Lozner<sup>6</sup> in which they present a different type of dilution technic for determination of prothrombin by the one stage method. These workers have expressed the belief that their procedure will enable one to detect changes in prothrombin concentration which ordinarily would not be recognized, and our experience would support their conclusions.

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<sup>6</sup> Kark, R., and Lozner, E. L. Nutritional Deficiency of Vitamin K in Man, *Lancet* 2 1162, 1939.



# LOCALIZATION OF STAPHYLOCOCCI IN AREAS OF INFLAMMATION PRODUCED BY XYLENE

R H RIGDON, M D

MEMPHIS, TENN

The phrase "locus minoris resistentiae" is hoary with years, and the initiation of local infective processes by injury unaccompanied with direct infection is a widely recognized fact<sup>1</sup> Streptococci, when given intravenously, have been observed to localize in abscesses produced by subcutaneous injection of silver nitrate<sup>2</sup> Benians<sup>3</sup> found that *Bacillus typhosus*, when injected intravenously in rabbits, localized in areas of skin where agar, mucin and starch had previously been injected Tubercle bacilli, when present in the blood stream, tend to localize in areas of necrosis and also in tissue showing an increase in vascularity<sup>4</sup> As early as 1843, Cazenave<sup>5</sup> observed that localization of a secondary syphilitic lesion is commonly determined by some concomitant irritation or morbid condition

Findlay,<sup>6</sup> in 1928, studied the problem of localization of bacteria in areas of injury He stated

When bacteria are present in the blood stream, their passage through the wall of the capillaries is difficult, except at those points where there is increased permeability (and probably also increased stickiness) of the capillary endothelium At these points organisms, therefore, tend to pass through the capillary endothelium and collect in the surrounding tissues The localization of organisms in injured tissues is thus dependent on a change in permeability of the capillary endothelium The subsequent development of a lesion in the tissues is conditioned by

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From the Department of Pathology, University of Tennessee Pathological Institute

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2 Sager, W W, and Nickel, A C Localization of Bacteria in Tissues of Lowered Resistance, Arch Surg **19** 1086 (Dec., pt. 1) 1929

3 Benians, T H C Septicemia The Selective Deposition of Colon Typhoid Group of Bacteria in Fixation Abscesses, Brit J Exper Path **2** 276, 1921

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5 Cazenave, P L A, and Schedel, H E Manual of Diseases of the Skin translated by T H Burgess, New York Samuel S Wood & William Wood 1852

6 Findlay, G M Histamine and Infection, J Path & Bact **31** 633, 1928

the number and virulence of the organisms which have passed through the permeable capillary wall and on the state of the surrounding tissue cells

The localization and concentration of trypan blue, india ink, staphylococcus antitoxin and the virus of vaccinia in areas of inflammation produced by local application of xylene have recently been studied.<sup>7</sup> It was found that each of the aforementioned substances localized and concentrated in areas of inflammation only during a specific interval after application of the irritant. Furthermore, the localization and concentration of trypan blue, india ink, staphylococcus antitoxin and the virus of vaccinia were not determined by either the presence or the absence of either edema or hyperemia.

In the present experiment an attempt has been made to study the mechanism by which staphylococci localize in areas of inflammation.

#### MATERIAL AND METHODS

The staphylococci were grown on the surface of agar in large flat bottles for twenty-four to forty-eight hours. The bacteria were then carefully scraped away, washed three times in large volumes of saline solution and suspended in physiologic solution of sodium chloride. The suspension of staphylococci was heavy enough to appear milky white. Ten cubic centimeters of this suspension was injected into the marginal vein of the ear.

Both sides and the abdomen of the rabbit were carefully shaved twenty-four hours or longer before the experiment was begun. Xylene was gently applied on a cotton swab to local areas of skin approximately 2 by 2 cm at varying intervals before the bacteria were given. In one part of this experiment xylene was applied to several areas of skin at the same time, immediately before the staphylococci were injected.

The rabbits either died or were killed at specific intervals after injection of the bacteria. Each area of skin treated with xylene was removed and divided into two portions, one of which was placed immediately into a 10 per cent concentration of solution of formaldehyde U S P, and the second of which was put into the incubator (37.5 C) for two to six hours, after which time it was removed and placed in a similar concentration of formaldehyde.

Areas of skin from the rabbits in which the xylene was applied to several areas at the same time were excised at intervals varying from forty minutes to six hours. The tissue was divided, one half was placed immediately into the solution of formaldehyde, and the second half was put into the incubator for six hours before it was put into the same preservative.

Sections of the skin were prepared in paraffin. They were stained routinely with hematoxylin and eosin. Select sections were stained by Giemsa's method to demonstrate the staphylococci.

#### RESULTS

Xylene was applied to the skin of 6 rabbits at the following intervals before the saline suspension of staphylococci was given: area 1, twenty-four hours; area 2, five hours; and area 3, immediately. The rabbits were killed one and one half

<sup>7</sup> Rigdon, R. H. Capillary Permeability in Areas of Inflammation Produced by Xylene, Arch Surg 41:101 (July) 1940.

hours later Sections of the skin were removed for histologic study Portions of the skin were kept in the incubator for only two hours in this part of the experiment

The degree of injury produced by xylene was relatively uniform in the different areas of skin of the same rabbit and also in different rabbits The skin usually became hyperemic within two to three minutes after application of this irritant, and frequently it was edematous within five minutes The edema and hyperemia remained for several days, after which time the epithelium desquamated Polymorphonuclear leukocytes apparently began to infiltrate the corium within ten to fifteen minutes after the xylene was applied Usually, however, one and one-half hours elapsed before any significant number of leukocytes reached this tissue Polymorphonuclear leukocytes and mononuclear cells continued to infiltrate the xylene-treated areas of skin for ten to twelve hours At this time many of the superficial epithelial cells separated from the basement membrane, and the spaces were filled with fluid and leukocytes The number of leukocytes apparently did not increase after the first thirty hours<sup>7</sup>

A few cocci were present in the lumens of the small blood vessels in those sections of skin where xylene was applied immediately before the staphylococci were injected Some of the bacteria were located in the cytoplasm of a few of the polymorphonuclear leukocytes present in the lumens of the blood vessels The number of organisms was much greater in the sections that were incubated than in those placed immediately in solution of formaldehyde Only an occasional coccus was found extravascularly Some of the staphylococci appeared to be in the cytoplasm of the endothelial cells lining the small blood vessels in the corium

It seemed likely that the number of bacteria could be increased and their location more easily determined by keeping the skin in the incubator for a longer time To determine whether this was true, xylene was applied to the skin of 2 rabbits in one area eight hours before the bacteria were injected and in a second area immediately prior to inoculation One of these rabbits died five minutes after injection of the staphylococci, and the second animal was killed after thirty minutes One half of each of the xylene-treated areas of skin was fixed immediately in solution of formaldehyde, while the second half was put into the incubator for five hours before it was put into a similar solution

Histologic studies showed many leukocytes in the corium in those areas of skin where xylene was applied eight hours prior to injection of the bacteria An occasional staphylococcus was observed in the cytoplasm of some of the polymorphonuclear leukocytes present in the lumens of the blood vessels and also in some of the extravascular leukocytes Organisms were present in the cytoplasm of the endothelial cells lining the wall of the small blood vessels in the corium immediately below the squamous epithelium in those areas of skin where xylene was applied immediately prior to injection of the staphylococci The small blood vessels appeared to be distended with staphylococci in those sections where the xylene was applied immediately before the bacteria were injected and the tissues were put into the incubator (fig 1 *B*) Those sections of skin to which xylene was applied eight hours before the organisms were given and which were placed in the incubator for six hours showed essentially no staphylococci, however, there were many leukocytes (fig 1 *A*)

*Comment*—The preceding experiments show that staphylococci, after an intravenous injection, localize and concentrate in areas of skin where xylene is applied only during a specific period after application of the

irritant The bacteria remain primarily within the lumens of the small blood vessels in the corium (fig 2) Some of the cocci appear to be within the cytoplasm of the endothelial cells lining these blood vessels Cocci are also present in the cytoplasm of many of the leukocytes in the lumens of the blood vessels A few leukocytes in the extravascular tissue have staphylococci within their cytoplasm

In an attempt to study further the mechanism by which staphylococci localize in areas of inflammation, xylene was applied to three areas of skin at the same time



Fig 1—*A*, xylene was applied to the rabbit's skin seven and one-half hours before 10 cc of a saline suspension of staphylococci was injected intravenously. This animal was killed thirty minutes later, and the xylene-treated skin was put into the incubator (37.5 C) for five hours. It was then fixed in a 10 per cent concentration of solution of formaldehyde U S P. There are a large number of polymorphonuclear leukocytes infiltrating the corium. *B*, the same rabbit as in *A* was used. Xylene was applied to this area of skin immediately before the staphylococci were injected. The tissue was treated like that shown in *A*. There are no polymorphonuclear leukocytes in the corium. The lumens of the small blood vessels are filled with staphylococci.

on each of 2 rabbits immediately before 10 cc of a saline suspension of staphylococci was given intravenously. The rabbits were anesthetized with ether 15 minutes later, and one of the xylene-treated areas of skin was removed (area 1). Two hours later a second area of the xylene-treated skin was removed (area 2).

One rabbit died ten minutes after removal of the second biopsy specimen. The third area of xylene-treated skin was removed four hours and forty minutes after injection of the staphylococci (area 3). The procedure for preserving these pieces of skin was the same as that used in the preceding experiments. The skin was kept in the incubator for six hours.

The sections of skin had no leukocytes in any of the three areas of tissue where xylene was applied, although the tissues remained in the animals sufficiently long, apparently, for these cells to reach the areas of inflammation (fig 3, A, C and E).



Fig 2—Xylene was locally applied to the skin of a rabbit immediately before 10 cc of a saline suspension of staphylococci was given intravenously. This section was removed two hours and forty minutes later. It was placed in the incubator for six hours and then fixed in solution of formaldehyde. The lumens of the small blood vessels immediately beneath the squamous epithelium are filled with staphylococci. Vessels of similar size in other portions of this section do not have any bacteria within their lumens.

A few cocci were present in the lumens of the small blood vessels in the corium in the sections of skin removed forty minutes after intravenous injection of the bacteria. The portion of skin removed at this time and put into the incubator

showed the bacteria usually in the small blood vessels in oval or rounded masses. These collections of organisms frequently were so dense that it was impossible to see the capillary wall (fig 3 B)

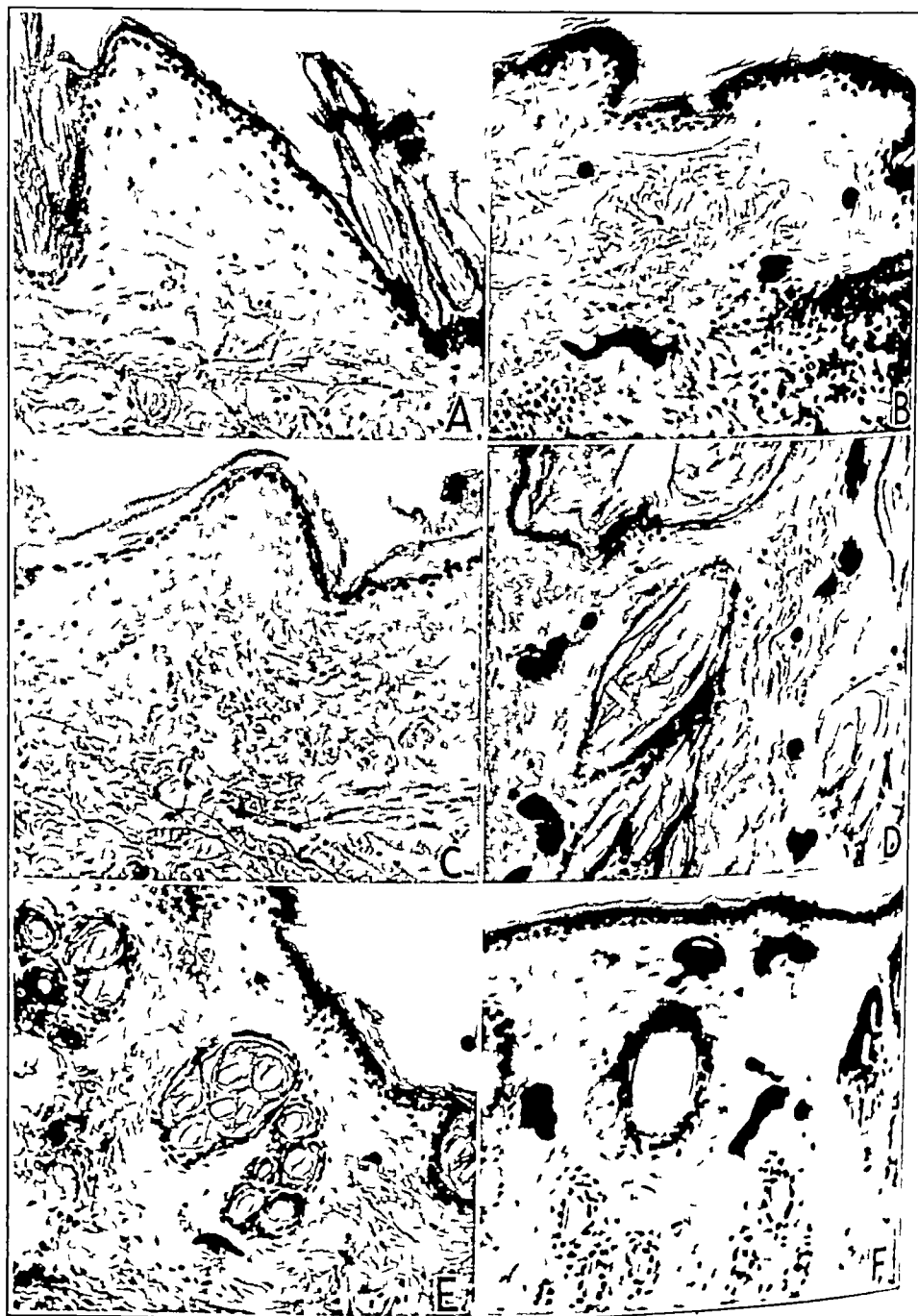


Figure 3

(See legend on opposite page)

The skin from area 2, removed two hours and forty minutes after intravenous injection of the staphylococci, showed essentially the same changes as the section removed after forty minutes (fig 3 C). There was, however, a greater number

of cocci in the former. Some of the bacteria appeared to be within the cytoplasm of the endothelial cells. The corresponding half of the section of skin put into the incubator showed a greater number of cocci than were observed in the tissues removed after forty minutes and incubated for a similar period (fig 3 *D*).

The skin from area 3, removed four hours and forty minutes after the organisms were injected, showed many of the small blood vessels to be filled with staphylococci (fig 3 *E*). The bacteria were in the lumens and in the cytoplasm of the endothelial cells. A few cocci were present around the periphery of the small blood vessels. The portion of skin removed at this time and put into the incubator showed the bacteria extending out from the vessel walls into the surrounding tissues (fig 3 *F*).

#### GENERAL COMMENT

Staphylococci, after an intravenous injection, localize in areas of inflammation in the rabbit's skin only during a specific period after local application of xylene. The localization of these organisms in areas of inflammation is not determined by either the presence or the absence of hyperemia and edema. The time in which the cocci localize in the tissues corresponds to that observed in a recent study on the localization and concentration of trypan blue, staphylococcus antitoxin, india ink and the virus of vaccinia in areas of inflammation produced by local application of xylene to the skin of the rabbit.<sup>7</sup>

The staphylococci are located most frequently in the lumens and in the cytoplasm of the endothelial cells lining the walls of the small blood vessels in the corium. Only a few cocci are present in the extravascular tissues, and they are adjacent to the walls of the blood vessels. These observations suggest that staphylococci circulating in the blood may be phagocytosed by the endothelial cells lining the walls of the small blood vessels in the corium. The cocci may not reach the extravascular tissue until the endothelial cells are severely injured by the staphylococci.

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Fig 3—The sections of skin ( $\times 220$ ) shown in this group are from the same rabbit. The tissues shown in *B*, *D* and *F* were put into the incubator for six hours before they were put into a 10 per cent concentration of solution of formaldehyde U S P. The rabbit was anesthetized with ether when each of the three sections of skin was removed. *A* This area of skin was removed forty minutes after injection of the staphylococci. Note the absence of either staphylococci or leukocytes in the corium. *B* Same as *A*, except that this section was put into the incubator. The lumens of many of the capillaries are filled with staphylococci. *C* This section of skin was removed two hours and forty minutes after the staphylococci were injected. Note the absence of both leukocytes and staphylococci in the corium. *D* Same as *C*, except that this section was put into the incubator. The lumens of the small blood vessels are filled with staphylococci. *E* This section of skin was removed four hours and forty minutes after the staphylococci were given. The lumens of some of the small blood vessels are filled with staphylococci. There are no leukocytes in this section. *F* Same as *D*, except that this section was put into the incubator. There are many more bacteria here than in section *E*.

It appears very unlikely that a nonmotile bacterium the size of a staphylococcus can pass extravascularly in a manner similar to that of a colloid

There is a difference of opinion as to the mechanism by which particles localize in areas of inflammation. Such localization may result from active phagocytosis by the endothelial cells. McJunkin<sup>8</sup> stated that granules of india ink appear in endothelial cells as a result of a transit of these granules through the cells and not as the result of active phagocytosis. Lang<sup>9</sup> found that carbon particles adhere to the inner surface of the capillary endothelium only in inflamed tissues. Later they appear within the endothelial cytoplasm, and at the end of ten hours some of the particles are present in the perivascular macrophages.

The phagocytosis of bacteria and inert particles by polymorphonuclear leukocytes during circulation in the blood has been observed.<sup>10</sup> The finding of staphylococci in the cytoplasm of the leukocytes, both intravascular and extravascular, in this study suggests that these bacteria may be carried through the blood vessel walls in leukocytes as the latter enter the areas of inflammation. Calumette<sup>11</sup> discussed dissemination of tubercle bacilli through the body by leukocytes. Goodpasture<sup>12</sup> recently suggested that typhoid bacilli may be carried from the intestinal tract to other organs by plasma cells.

Two methods, therefore, apparently are available by which staphylococci may reach the extravascular tissues in areas of inflammation. In one the organisms either adhere or are phagocytosed by the endothelial cells. The bacterium may then reach the extravascular spaces only after the endothelial cells are severely injured. The second method consists in active phagocytosis of the bacteria in the circulating blood by the leukocytes and passage of the organism through the capillary wall within the cytoplasm of the leukocytes. The cell is then destroyed by the staphylococci. It appears to me likely that the latter method occurs more often than the former when there are only a few staphylococci in the circulating blood.

It is interesting to observe that only the small blood vessels in the corium show any staphylococci (fig. 2). Vessels of similar size in the adjacent muscle and fat do not show any cocci within their lumens.

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There is nothing in this study to indicate why staphylococci either stick or are phagocytosed by the endothelial cells during only a specific interval after local application of xylene. This same phenomenon has been observed with several substances very different from bacteria.<sup>7</sup>

There is apparently no satisfactory explanation at this time for the cellular changes that occur in inflammation. Menkin's<sup>13</sup> preparation, leukotaxine apparently will not explain this phenomenon. Several investigators have already shown that a substance may be obtained from normal tissues which when injected intradermally permits localization and concentration of an intravenous injection of trypan blue in the skin of the rabbit.<sup>14</sup>

The absence of polymorphonuclear leukocytes in the corium in the xylene-treated areas of skin of the 2 rabbits given intravenous injections of staphylococci at the time the irritant was applied is most interesting (fig. 3), since the skin of all the other rabbits studied to which xylene was applied several hours before the staphylococci were injected intravenously showed a large number of leukocytes in the corium. The ether used for anesthesia may have played some role, however, at this time such a factor appears insignificant.<sup>15</sup>

#### SUMMARY

Staphylococci, after intravenous injection, localize in areas of inflammation in the skin of the rabbit only during a specific period after local application of xylene. The localization of these organisms in areas of inflammation is not determined by either the presence or the absence of hyperemia and edema.

A majority of the bacteria apparently remain within the lumens and in the endothelial cells of the small blood vessels in the corium.

There appear to be two ways in which staphylococci may reach the extravascular tissues in areas of inflammation. 1 The organisms may be phagocytosed by polymorphonuclear leukocytes while they are in the lumens of blood vessels and may be carried through the vessel wall within the cytoplasm of these cells. 2 The organisms may either adhere or be phagocytosed by the endothelial cells, after which the cells are severely injured by the bacteria, thus permits the latter to reach the extravascular tissue.

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# CANCER OF THE TONGUE

HAYES E MARTIN, M D

Attending Surgeon, Memorial Hospital for the Treatment of Cancer  
and Allied Diseases

HILMAR MUNSTER, M D †

AND

EVERETT D SUGARBAKER, M D \*

NEW YORK

Cancer of the tongue causes more deaths than any other of the malignant growths of the head and neck, and therefore it must be considered the most important tumor in that group. In comparison with other malignant growths of the upper respiratory and alimentary tracts, it is only slightly less malignant than the highly anaplastic and rapidly growing tumors of the oropharynx and nasopharynx. Excluding cancer of the lip, it is more frequent than any other single anatomic variety of cancer in this region.

The records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases contain over 1,500 cases of cancer of the tongue, but since many of the older records are incomplete, we have utilized for the purpose of this report only the cases of patients admitted during the eight year period, 1927 to 1934 inclusive. This series (556 cases) comprises a consecutive group of all patients with cancer of the tongue, histologically proved, who applied to the clinic during the above mentioned period, except those in whose cases the period of observation was less than one month, owing to the patient's inability or unwillingness to return for either curative or palliative treatment. Our records show that less than 1 of 20 patients with cancer of the tongue who apply to our clinic is unable or unwilling to return. No cases have been excluded from the series because of the advanced stage of the disease.

The standards used in the makeup of this series are described in greater detail under the discussion of end results at the conclusion of

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From the Head and Neck Service, Memorial Hospital

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Nov. 20, 1936

† Former Rockefeller Fellow in Cancer Research, Memorial Hospital for the  
Treatment of Cancer and Allied Diseases. Dr. Munster died Dec. 21, 1939.

\* Rockefeller Fellow in Cancer Research, Memorial Hospital for the Treatment  
of Cancer and Allied Diseases

this paper In this communication, we have attempted to overcome the deficiencies common to most published reports on cancer of the tongue, which, as a rule, deal only with selected groups of tumors in early stages treated by a single method, usually surgical, and which therefore do not represent true samples of lingual cancer as this disease exists at the present time

*Definition*—The term "cancer of the tongue" as used in the present report comprises all malignant growths arising in the organ from the valleculae to the tip, including the under surface anteriorly and laterally In some clinics, those growths which originate in the floor of the mouth anteriorly and laterally are also classified as lingual cancers It is our opinion that such a comprehensive use of the term "cancer of the tongue" is not advisable, since the floor of the mouth is a separate anatomic structure, and growths of this region, although resembling somewhat those of the under surface of the tongue, possess individual clinical and anatomic characteristics deserving of a separate classification

#### ETIOLOGY

*Incidence*—Cancer of the tongue is one of the most common anatomic forms of malignant growth of the oral cavity At the Memorial Hospital it comprises about 15 per cent of all tumors of the upper respiratory and alimentary tracts and about 25 per cent of all intra-oral tumors According to recently calculated mortality statistics furnished us by the department of health of New York city,<sup>1</sup> cancer of the tongue caused 1.2 per cent of all deaths from cancer It is probable, however, that not all deaths due to cancer of the tongue are reported as such This is particularly likely to be true of cancer of the base of the tongue, which is difficult to diagnose and is often confused with cancer of the pharynx From our own and various other statistical data, we estimate that cancer of the tongue makes up between 2 and 3 per cent of all human cancer

*Age*—In the series herein reported, the average age of the patients was about 58 years at the time of admission to the hospital, which runs fairly close to our figures for such other forms of intraoral cancer as cancer of the cheek (59 years) and cancer of the lip (57 years) Our mean age incidence is about five years higher than that calculated by Lane-Clayton<sup>2</sup> from over 30 separate reports totaling over 1 000 cases There are many reports in which the mean age incidence of cancer of the tongue is given as over 60 years, but there is general

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<sup>1</sup> Duffield, T Personal communication to the authors

<sup>2</sup> Lane-Clayton, J E Report on Cancer of the Lip Tongue and Skin Ministry of Health Reports on Public Health and Medical Subjects no 59 London, His Majesty's Stationery Office, 1930

agreement within the range of 55 to 60 years, with a greater incidence between the ages of 60 and 64 than in any other five year period. The age of the oldest patient in the present series was 89 years, while that of the youngest was 17.

*Sex*—In this series, 87 per cent of the patients were males and 13 per cent females. Other statistics of our clinic have shown that the incidence of cancer of the tongue in females is greater than that of either cancer of the lip (6 per cent) or cancer of the cheek (10 per cent).

*Position of the Growth*—The topographic distribution of cancer of the tongue in our clinic varies considerably from that indicated by most of the figures reported in the literature, although there is general agree-

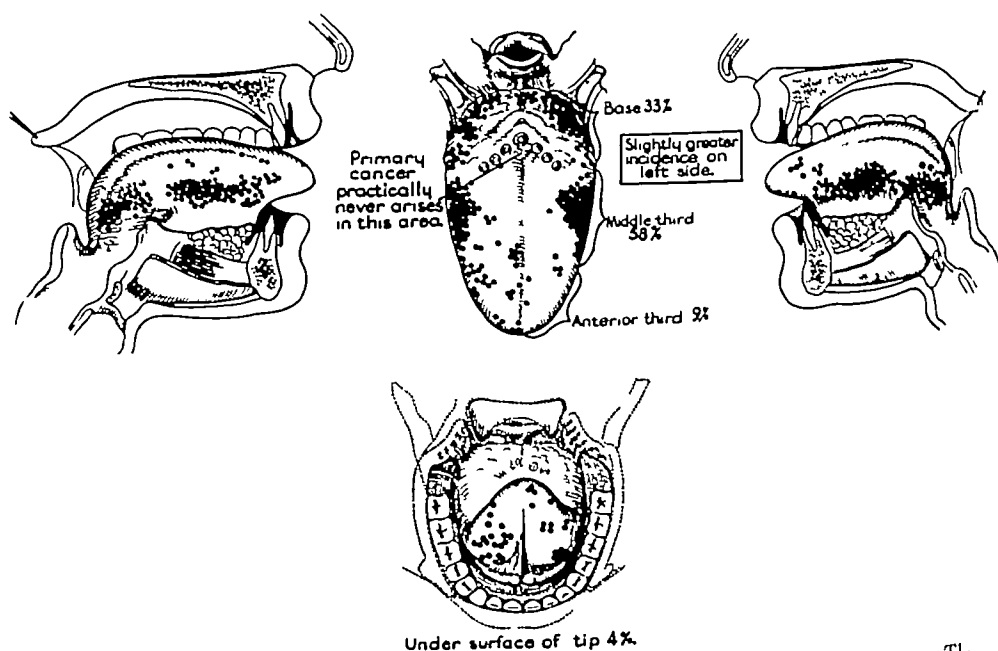


Fig 1—Topographic distribution in 673 cases of cancer of the tongue. The lateral border of the middle third is the most common site of origin (58 per cent) with the base of the tongue next in frequency (33 per cent). The dorsum at the line of the circumvallate papillae has never been the site of primary cancer in our experience.

ment that the most frequent site of origin is the edge of the tongue in its middle third (50 per cent in our series). The incidence in other regions is shown in figure 1. The lack of any standard classification and uniform demarcation of boundaries with regard to these other reports makes it rather difficult to compare the published figures in the various reports. This question is of little practical importance except in reference to the relative percentage of cancer of the base of the tongue. In this area, the marked discrepancies of the various reports can indicate only that cancer of the base of the tongue is not always included in the average report of lingual cancer. The diagnosis may be

entirely, owing to the indefinite character of the local symptoms and the moderate difficulty of physical examination, or the growth may be classified as pharyngeal rather than lingual, as MacFee<sup>3</sup> and Roux-Berger have pointed out. Furthermore, even though correctly diagnosed, cancer of the base of the tongue would usually be considered inoperable and for that reason would tend to be omitted entirely from strictly surgical reports.

The incidence of intraoral cancer in general seems to be greater on the left side than on the right, the ratio approaching 60:40, as has been reported repeatedly.<sup>4</sup> In a recent series of 252 cancers of the lip at Memorial Hospital, 57 per cent were recorded as occurring on the left, and twice as many on the left side of the upper lip as on the right side of the upper lip. The dorsum of the middle third of the tongue, especially that region just in front of the lingual V, seems to be singularly immune to the development of the initial lesion in cancer. The records of about 1,500 cases of cancer of the tongue at Memorial Hospital in no instance show the growth to have arisen in this region. This point will be discussed further under differential diagnosis.

*Causative Factors*—As in other forms of cancer of the oral cavity proper, chronic irritation is an outstanding apparent etiologic factor in growths of the middle and anterior thirds of the tongue. In these areas, such precancerous changes as chronic diffuse or localized glossitis and leukoplakia most often occur. At the base of the tongue (lingual tonsils and valleculae), tissue changes as a result of chronic irritation are less definite, even in the most aggravated chronic glossitis, and are usually evidenced by an injection of the mucous membrane, an increase of lymphoid tissue and an irregularity of the mucous surface. So far as we know, leukoplakia of the tongue is never seen posterior to the lingual V. This portion of the tongue is rather well protected from several of the common forms of chronic irritation, and on first thought one might conclude that this etiologic factor is of only minor importance in cases of cancer of the base of the tongue. There is definite evidence, however, that some forms of tobacco smoking are particularly apt to cause cancer in this region.

The average wear on the teeth and the response of the soft tissues to the normal environment—eating, drinking and speaking—constitute

3 MacFee, W. F. Concealed Cancer of the Tongue, *Ann Surg* **93** 481, 1931.  
Roux-Berger, J. and Jadlovker, M. L'envahissement lymphatique dans les cancers de la base de la langue, *Presse med* **48** 249, 1940.

4 (a) Broders, A. C. Squamous Cell Epithelioma of the Lip, *J. A. M. A.* **74** 656 (March 6) 1920. (b) Butlin, H. T. Diseases of the Tongue, ed. 1 London, Cassell & Co., 1885. Butlin, H. T. and Spencer, W. G. Diseases of the Tongue, ed. 2 London, Cassell & Co. 1900. (c) Regaud, C. Radium Therapy of Cancer at the Radium Institute. *Am. J. Roentgenol* **21** 1 1929.

a definite though mild chronic irritation, but it is not with such a degree of irritant effect that this discussion is concerned. By the term "chronic irritation" as hereinafter used is meant the physiologically demonstrable abnormal effects which occur as the result of chronic trauma.

Such characteristic signs of chronic irritation in the oral cavity as leukoplakia, chronic glossitis and dental sepsis are much more prevalent in the male than in the female. The fact that cancer of the oral cavity is likewise more frequently found in the male is one of several evidences of a direct causal relationship between chronic irritation and intraoral cancer. Ahlbom's<sup>5</sup> investigations indicate that tobacco, syphilis and achlorhydric anemia with the Plummer-Vinson syndrome are outstanding etiologic factors in intraoral and pharyngeal cancer in Sweden.

Undoubtedly the chronicity of the irritant is more important than its nature. Most of the anatomic forms of cancer which follow chronic irritation (cancer of the skin, lip, cheek, etc.) are more common in the aged, in whom the irritant has had sufficient time to act. No one specific form of chronic irritation per se appears to be of singular importance in the etiology of cancer. It is more logical to assume that cancer genesis results from the cumulative effect of several forms of irritation. A single acute trauma to the tongue is occasionally alleged to have produced cancer, but this supposition probably has little merit.

*Syphilis*—Routine Wassermann tests in our clinic reveal that about 33 per cent of our patients with cancer of the tongue also have syphilis. An incidence (higher in males than in females) of 30 to 40 per cent of syphilis as shown by positive Wassermann reactions is found in most reported series in which this question has been investigated.<sup>6</sup> Beeson<sup>7</sup> in reporting a general average incidence of 30 per cent of syphilis in cases of cancer of the tongue, found 35 per cent in men and 6 per cent in women and compared this figure with an incidence of positive Wassermann reactions of about 5 per cent which he found in general hospital admissions and of about 7 per cent in cases of cancer in general.

In our series, the average age for cancer of the tongue in syphilitic persons was the same as in nonsyphilitic persons, while Belote<sup>6</sup> found an average age incidence for cancer of the tongue in syphilitic men of 54 years as opposed to 62 years in nonsyphilitic patients. Schreder<sup>8</sup>

5 Ahlbom, H. E. Prädisponierende Faktoren für Plattenepithelkarzinom im Mund, Hals und Speiseröhre. Eine statistische Untersuchung am Material des Radiumhemmets, Stockholm, Acta radiol. **18** 163, 1937.

6 (a) Belote, G. H. Association of Carcinoma of the Tongue and Syphilis as Determined by Positive Serologic Tests, J. A. M. A. **94** 1985 (June 21, 1928).

(b) Bloodgood, J. C. Cancer of the Tongue. A Preventable Disease, Brit. J. Radiol. **31** 81, 1926. (c) Quick, D. Treatment of Cancer of the Tongue.

7 Beeson, B. B. Cancer of the Tongue and Syphilis, U. S. A. **40** 565, 1936.

and Brown<sup>8</sup> found 40 per cent of cancers of the tongue to be associated with positive Wassermann reactions. It is interesting to compare the incidence of syphilis associated with cancer of the tongue as found by Kaplan<sup>9</sup> (41 per cent) at Bellevue Hospital, New York, where the patients are mainly drawn from an urban population of the less fortunate economic levels, with that of Spencer,<sup>10</sup> who in a distinctly rural population (Boulder, Colo.) found only 1 in 14 patients to have a positive Wassermann reaction. Even though the latter number of patients is small, the smaller incidence of syphilis is highly suggestive.

The immediate etiologic factor in these cases is undoubtedly the chronic glossitis so characteristic of late syphilis. Neither acute syphilis nor the constitutional effect of this disease has any bearing on the etiology of cancer, nor do we believe that there is any specific cancerigenic influence involved. The etiologic significance of syphilitic glossitis probably lies mainly in its chronicity and its frequency. The attendant degenerative changes, such as atrophy of the papillae and leukoplakia, are so characteristic that they have often been considered diagnostic of syphilis.

*Nonsyphilitic Glossitis*—One of the most widely known objective symptoms of derangement of function of the gastrointestinal tract is the appearance of the tongue. The brownish coated tongue of chronic constipation and acute indigestion and other forms of chronic glossitis and bald tongue, such as those associated with achlorhydria, pernicious anemia, sprue, pellagra, etc., are well known. More recently, those disorders associated with avitaminosis and dysfunction of the liver have been found to produce profound changes in the lingual mucosa. Many of these degenerative changes are so similar to those produced by syphilis as to be indistinguishable from them except by the Wassermann test. Several of these diseases tend to be self limited, however, by reason of their gravity, so that chronicity, which is essential for the development of cancer, is not characteristic.

*Leukoplakia*—In susceptible subjects, chronic irritation of the mucous membrane may result in the development of either leukoplakia or cancer or of both in the same patient. When the two conditions

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8 Schremer, B. F., and Brown, H. F. R. An Investigation of the Results Obtained in Cancer of the Tongue Treated by Radium and Roentgen Rays, *Am. J. Roentgenol.* **15** 207, 1926. Schremer, B. F. Five-Year End-Results of Radiation Treatment of Cancer of the Oral Cavity, Nasal Pharynx and Pharynx. *Radiol. Rev. & Chicago M. Rec.* **51** 327, 1929.

9 Kaplan, I. I. Treatment of Cancer Patients, *New York State J. Med.* **36** 5, 1936.

10 Spencer, F. R. Carcinoma of the Tongue. Review of Fourteen Cases. *Arch. Otolaryng.* **24** 1 (July) 1936.

are associated, the leukoplakia ordinarily precedes the cancer, but one occasionally observes the reverse, that is, leukoplakia developing after the treatment of a cancer of the tongue when none had been present before

Malignant degeneration may occur within a patch of leukoplakia, or the growth may develop in apparently normal mucous membrane of the tongue at a distance from leukoplakic areas on the cheeks or lips. Pre-existing leukoplakia may not be apparent in cases in which a cancerous ulcer has eroded or engulfed a leukoplakic patch. Lingual cancer arising on the basis of advanced leukoplakia commonly begins on the dorsum and is apt to be multiple. We have observed 1 patient in whom three separate primary lesions (not recurrences in a single area) developed on a leukoplakic tongue over a period of about six weeks. Multiple tumors may occur at longer intervals, for instance, a man who was treated at the Memorial Hospital in 1922 for a cancer of the left border of the tongue returned in 1940, at the age of 70, with a cancer of the opposite side of the tongue. In our clinic, some degree of leukoplakia was specifically noted in about 46 per cent of all cancers of the tongue.

*Tobacco*—It is difficult to estimate the degree of influence of tobacco in the etiology of cancer of the tongue. In our male group, about 75 per cent of patients admitted the moderate to heavy use of tobacco at some time during their adult life, but this figure loses most of its significance in view of the fact that the general adult male population appears to be addicted in at least as high a percentage. The lesser susceptibility of the female to intraoral cancer has often been ascribed to a lesser indulgence in the tobacco habit. In our series, only 9 per cent of the women admitted smoking, as compared to 75 per cent of the men. Nevertheless, if one considers only the nonsmokers of both sexes, the disease is still more than twice as frequent in the male as in the female.

*Teeth and Artificial Dentures*—In the sixth and seventh decades when the incidence of intraoral cancer is greatest, a large percentage of the general population has suffered dental diseases and defects for prolonged periods. The presence of these dental defects, however, may be coincident with the "cancer age" rather than a direct cause of cancer. As with tobacco, the ubiquity of these dental factors in the whole population renders it impossible either to affirm or to deny their etiological significance. In only about 10 per cent of our patients with intraoral cancer were the teeth found to be clean and in good repair, and in all patients dental defects and sepsis were almost the rule.

In a few instances the association of direct dental trauma with growth is evident. The most obvious form of dental irritation is the presence of a sharp tooth, broken or worn, or of an ill fitting denture directly in contact with a carcinomatous ulcer, which occurs



approximately 10 per cent of our patients. In certain instances the experienced observer will suspect that a supposedly guilty tooth or denture may have become "irritating" or "ill fitting" after and because of the development of a cancerous growth, rather than vice versa. Less direct dental abnormalities noted in our patients were advanced dental caries and pyorrhea.

#### PATHOLOGY

Differentiating, keratinizing squamous carcinomas and relatively non-keratinizing mucous membrane types of epidermoid carcinoma comprise about 90 per cent of the malignant tumors of the tongue which occur anterior to the circumvallate papillae. About 80 per cent of carcinomas of the base of the tongue are of the nonkeratinizing variety, and in this region anaplastic tumors occur in larger proportion. Transitional cell carcinoma and lymphepithelioma comprise about 20 per cent of tumors at the base. Spindle cell epidermoid carcinomas occur in the tongue, but they are rare. Forms of adenocarcinoma, adenoid cystic adenocarcinoma and mucous gland adenocarcinoma, indistinguishable from various types of gastrointestinal cancer, may occur.

Sarcomas of the tongue are exceedingly rare, except for lymphosarcomas of the lingual tonsillar tissue. The clinical records of the Memorial Hospital contain but 1 case of probable muscle sarcoma. Repeated reference to sarcoma of the tongue may be found in the literature of the last fifty years, but in most cases it seems to us that the histologic verification is far from clear. The only clearly acceptable instances of true malignant myosarcoma recorded in the literature are the 2 described by Cappell and Montgomery,<sup>11</sup> in which the growths occurred in children, as did the one in our case. In any event, sarcoma of the tongue is so rare that it can have little or no influence on the statistics of cancer.

#### SYMPTOMS, MORBID ANATOMY AND CLINICAL COURSE

In general, lingual cancer tends to be practically symptomless in its early stages. The most common first symptom in our group of cases was the discovery by the patient of the primary lesion itself or of the metastatic node, and in over 50 per cent of the cases there was no complaint except of its physical presence. In the anterior two thirds of the tongue, the growth was usually discovered by the tactile sense as an irregularity or roughening of the mucous membrane.

Occasionally pain is a first symptom in cancer of the tongue, but it is remarkable that this symptom should not be complained of more often since most benign ulcerated lesions of the tongue are painful, for example, herpes or traumatic ulcers. It is probable that if the tumor

11 Cappell, D. F., and Montgomery, G. L. On Rhabdomyoma and Myoblastoma. *J. Path. & Bact.* 44: 517, 1937.

begins in the superficial layers and ulcerates early pain will be an early symptom, but in other instances the growth, even though ulcerated, takes the form of an epithelial covering and thereby protects the underlying sensory nerves from irritation sufficient to cause pain

In the majority of instances the patient discovers the lesion by the tactile and visual senses alone and not because of any actual discomfort. After this discovery, delay in seeking medical advice is due mainly to the fact that the average layman believes that a serious disease cannot exist in the absence of actual discomfort. Once initiated, the progress of the growth may be so gradual and insidious that it is accepted as a part of a long-standing chronic glossitis or oral dental sepsis. The posterior third, or base, of the tongue has little or no tactile sense and cannot be visualized by the patient, and growths in this region are therefore apt to reach a larger size or even to metastasize before producing symptoms sufficient to induce the patient to seek medical advice.

Other first symptoms, in the order of their frequency, are as follows: the development of palpable cervical nodes, hoarseness, dysphagia or dyspnea (when the base of the tongue is involved) and pain, tenderness or irritation ascribed to sharp teeth or ill fitting dental plates. The average duration of symptoms before admission was about seven months in the series herein reported, as compared to nine months for cancer of the cheek.

The manner of origin and subsequent development of the tumor may vary, depending on its exact site of origin, and we shall consider first the tumors of the anterior two thirds. In this region the most common form is a small, indurated, painless, nontender ulcer arising on the edge of the middle third of the tongue. Palpation reveals that the tumor is larger than it appears on inspection alone. As the lesion increases in size, the surface becomes raised and granular, the ulceration spreads and the infiltration deepens. Finally, the center becomes excavated, and when the growth has reached the size of 2 or 3 cm in diameter, deep erosion, fissuring and infection commonly occur, with pain and tenderness.

Until the disease has infiltrated about a third of the anterior portion of the tongue or until a fungating tumor 2.5 or 3 cm in diameter has developed, there is usually little actual discomfort or interference with function. In the later stages, when the muscular body of the tongue has become deeply involved and infiltrated by the growth and by sepsis, the organ lies practically immobile in the floor of the mouth. Surface necrosis is then apt to occur, with repeated hemorrhage due to erosion of the lingual artery or of its larger branches. Pain radiates to the ear or mastoid region, fetor oris and excessive salivation are distressing late symptoms.

*Symptoms of Cancer at the Base of the Tongue*—A primary lesion at the base of the tongue is not often discovered by the patient, who is therefore apt to seek medical advice first because of an enlarged cervical node. In the series herein reported, symptoms referable to the tongue or to the pharynx were unrecognized on admission by one third of all patients with cancer at the base of the tongue, since, even when present, such symptoms as slight soreness, dysphagia, hoarseness or dyspnea were apt to be vague and misleading. A cancer at the base of the tongue may ulcerate and reach a size of 3 cm or more without causing any particular noticeable local symptoms.

In over 30 per cent of cases of growths of the posterior third of the tongue, the referring physician had not discovered the primary lesion but had suspected cancer because of cervical adenopathy. A careful examination of patients referred because of cervical lymphadenopathy (nodes 3 to 4 cm in diameter or even larger) often discloses a primary lesion in the base of the tongue less than 1 cm in diameter, though in most instances it is over 2.5 cm in diameter when the first diagnosis of cancer is made.

*Morbid Anatomy*—Cancer of the tongue is almost always of epithelial origin and therefore begins on the surface. Unfortunately, one rarely has an opportunity to observe and describe the disease in its earliest stages. In our clinic, in the rare instances when the lesions were less than 5 mm in diameter, they almost all appeared as slightly ulcerated fissures in the center of preexisting leukoplakic patches (fig 2). It is certain, however, that the disease does not always begin in this manner. When the growth does not originate in a leukoplakic patch, it is probable that it begins as a microscopic submucous nodule and that the earliest departures from the normal are so slight as to preclude a diagnosis by physical examination until the growth has reached a size of 6 to 10 mm, with definite induration and ulceration.

Most of the earlier lesions are from 1 to 2 cm in diameter when first discovered and consist of a superficial, indurated plaque, slightly raised above the surface of the tongue, ulcerated in its center, with an irregular, nodular, coarsely granular surface (fig 3). In such lesions the induration extends several millimeters beyond the edge of the ulcer and the infiltration reaches a depth of 0.5 to 1 cm.

There may be considerable variation in the anatomy of tumors which have reached a size of 2 to 2.5 cm in diameter. At one extreme may be found papillary fungating lesions with only moderate infiltration, often slightly pedunculated, with marked eversion of the mucous membrane at its borders. The degree of fungation from the surface is usually inversely proportionate to the depth of the infiltration. At the other extreme are the deeply infiltrating and excavating lesions which

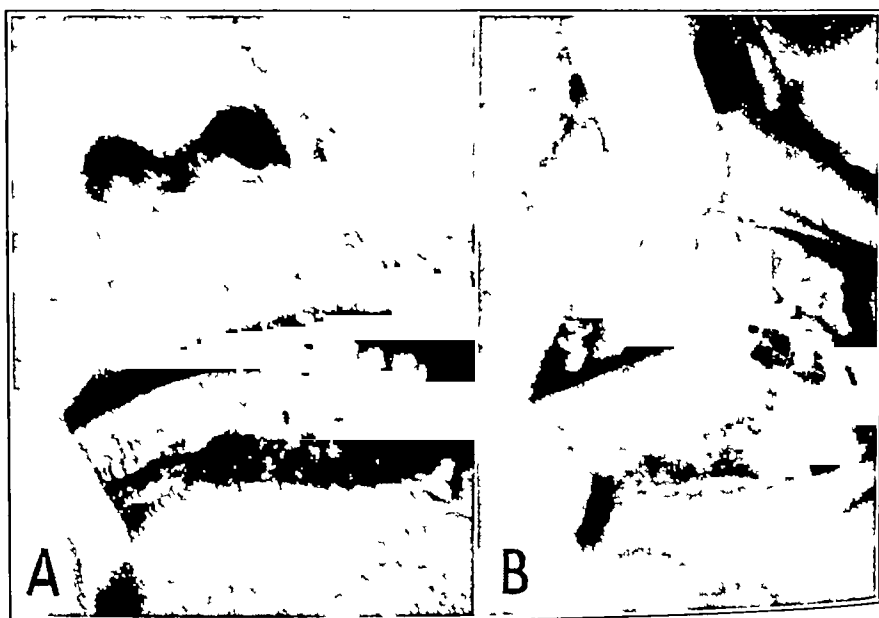


Fig 2—Very early cancer of the tongue arising in the center of an area of leukoplakia in the middle third of the lateral border (A) At this stage the chances of metastatic invasion of the cervical nodes are slight, and cure is almost certain with either irradiation or surgical treatment In this case, after biopsy the treatment was by the implantation of one radon seed of about 2 millicuries B, healed condition The patient has remained well for about eight years

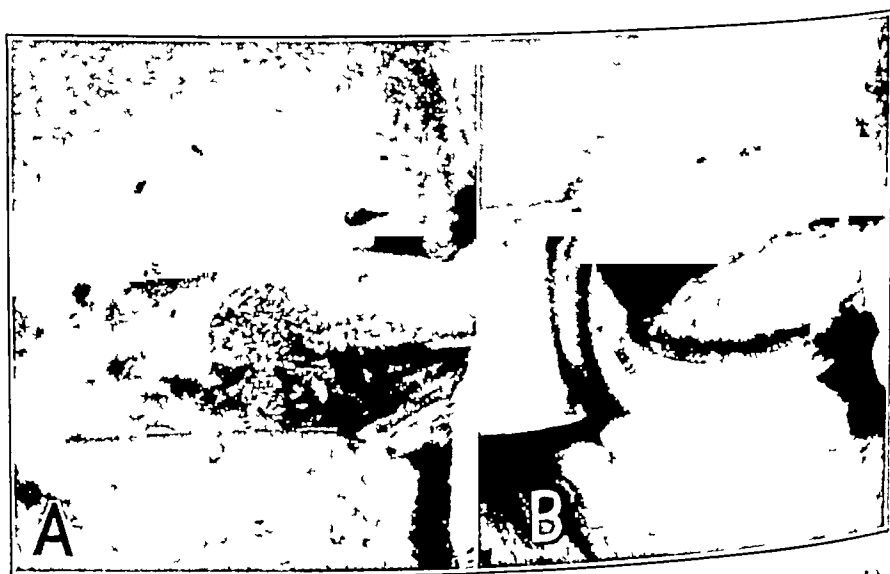


Fig 3—The average cancer of the tongue on the patient's admission to the hospital presents an ulcerated granular lesion 2 to 2.5 cm in diameter on the lateral border of the tongue in the middle third (A) At this stage, even though the cervical nodes are not palpably enlarged, metastases are actually present on admission in about 10 to 15 per cent of all cases, as shown by the later clinical course The preferable form of treatment for the primary lesion is irradiation B, healed condition after application of peroral roentgen radiation supplemented by radon seeds Since no cervical metastases were palpable, no treatment was given to the neck The patient has remained well for about six years

begin to erode the tongue substance in the early stages of infiltration. Midway between these extremes are found tumors which produce only moderate alteration of the normal contour of the lingual surface, although they ulcerate superficially and infiltrate deeply.

In other clinical forms the lesion may assume the character of a superficial ulceration which advances mainly at the edges, eroding the mucous membrane over an area 2 to 3 cm in diameter without infiltrating the lingual substance to a greater depth than 3 to 4 cm. In some instances the growth apparently arises in the deep layers of the mucous membrane or in fissures and extends and infiltrates deeply, so that a large tumor may occupy the body of the tongue with little or no surface ulceration. In the so-called scirrhus form the involved

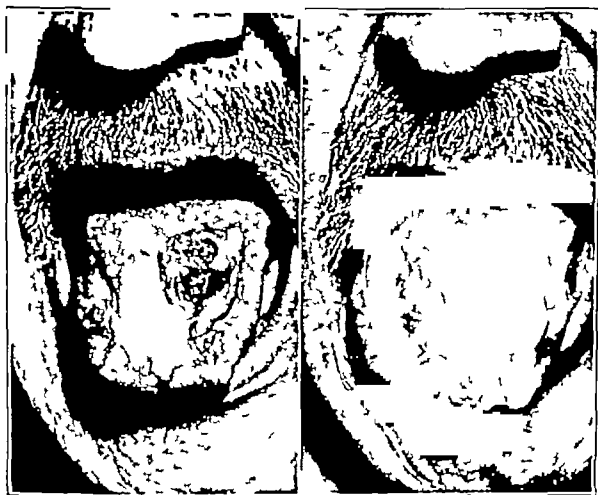


Fig 4—Cancer of the dorsum of the tongue is usually associated with leukoplakia, and there may be multiple primary lesions. The dorsum of the tongue is readily accessible to treatment by irradiation, and the prognosis is good except for the possibility of the development of additional growths in other areas. This patient had a cervical metastatic node in the left side of the neck, which after aspiration biopsy was treated by fractionated roentgen irradiation and implantation of radon seeds. The patient has remained well for over five years.

portion of the tongue is shrunk, sometimes to such an extent that in the advanced stages of the disease the whole organ seems to have disappeared.

Cancer developing on the basis of advanced leukoplakia may appear as a papillary, warty, nonulcerated growth, as an indurated, slightly ulcerated fissure in a leukoplakic patch or as a deep red superficial granular ulcer surrounded by leukoplakia (fig 4). When the cancer develops on the basis of a long-standing syphilitic glossitis (both superficial and interstitial), the tongue may be so swollen and edematous

that the jaws cannot be completely closed. In such instances the swollen bulk of the tongue may be due mainly to sepsis while the mass of the actual cancer is comparatively small (fig 5)

In the advanced stages more than one clinical variety may be present. The entire tongue may be infiltrated and boardlike, with surface ulceration over one or more areas 1 to 2 cm. in diameter, in other instances the growth may infiltrate deeply from its point of origin and appear on the surface in one or more additional areas by perforation of the mucosa from below.

*Metastases*—The comparative incidence of metastases on admission to the hospital with the more common forms of intraoral cancer is shown in table 1. In the series of cancers of the tongue reported here, the



Fig 5—Diffuse involvement of the tongue by cancer and interstitial syphilitic glossitis. Such lesions are not suitable for treatment by irradiation, and if the tongue is movable, they are sometimes best dealt with by subtotal glossectomy. This patient died of cervical metastases after several months without local recurrence following subtotal glossectomy.

TABLE 1—Incidence of Cervical Metastases of Intraoral Cancer Observed at the Memorial Hospital

Primary Lesion	Metastases on Admission	Metastases after Admission	Total Metastases	No. at Any Time
Tongue	35%	25%	60%	107
Lip	20%	8%	32%	67
Cheek	40%	10%	50%	40
Nasopharynx	77%	4%	81%	18

incidence of metastases on admission was about 39 per cent. Additional 24 per cent subsequently had metastases, making a total of 62 per cent with metastases at some time during the course of the disease.

The group of lymph nodes earliest and most frequently involved is the upper deep cervical (55 per cent), which is centered about at the bifurcation of the common carotid artery (fig 6). This area was eventually involved in 80 per cent of all cases of metastasizing cancer of the tongue in this series. When initial involvement of the cervical nodes is on the side of the neck opposite the primary lesion, the upper deep cervical nodes are almost always the first to be invaded. In the cases under consideration, bilateral metastases occurred in about 25 per cent of all lesions which metastasized. The sites next often involved, in the order of their frequency, are the submaxillary triangle (15 per cent) and the midneck (7 per cent). As the disease progresses, it extends to the other groups of nodes, and after the upper deep cervical nodes have been invaded, one should always be on the watch for enlarged nodes in the lower deep cervical region or in the posterior triangle of the neck.

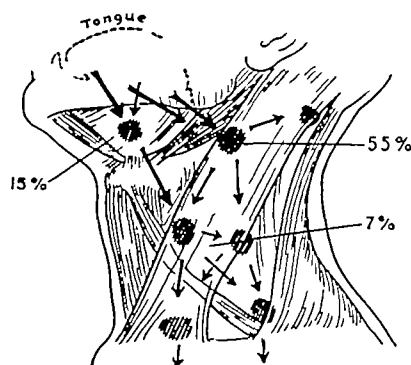


Fig 6—Pathways of metastasis in cancer of the tongue. The figures express the frequency of initial involvement in certain areas.

Dissemination below the clavicle to the viscera or other soft parts and to bone is far more frequent in cancer of the tongue than in cancer of the lip or cheek.<sup>12</sup> Visceral metastases are particularly likely to follow growths of the base of the tongue, where anaplastic tumors are common. In the autopsy records of the Memorial Hospital, it has been found that of about 68 patients dead of lingual cancer, 12 (18 per cent) had visceral metastases with the distribution shown in table 2. Ewing<sup>13</sup>

12 (a) Crile, G. W. Carcinoma of Jaws, Tongue, Cheek and Lips. *Surg Gynec & Obst* **36** 159, 1923. (b) Gernes, C., Breton, A., and Boury, M. Cancer du cou secondaire à un épithélioma de la langue cliniquement guéri par l'application de radium réflexions. *Bull Assoc franç p l'étude du cancer* **26** 58, 1937. (c) Lenz, M., and Sproul, E. Carcinoma of the Tongue. *Am J Surg* **35** 102, 1934. (d) Spencer, W. G., and Cade, S. Diseases of the Tongue, Philadelphia: P. Blakiston's Son & Co., 1931.

13 Ewing, J. Neoplastic Diseases, ed 3. Philadelphia, W. B. Saunders Company, 1928.

reported a case of diffuse permeation of pulmonary lymphatics from squamous carcinoma of the tongue

### DIAGNOSIS

A tentative diagnosis of cancer of the tongue is not difficult in the average case. Whenever chronic ulcers or indurated tumors occur in the tongue or any other part of the oral cavity, cancer should be suspected. Examination of the anterior two thirds of the tongue is easily performed under ordinary lighting assisted by the palpating finger. Examination of the base of the tongue should be performed by inspection with a headlight and a throat mirror, supplemented by careful palpation.

*Biopsy*—If a suspicious lesion is found, a biopsy should always be made at the time of the first examination. In any case, there is no excuse for a temporizing or passive attitude in the presence of a chronic

TABLE 2—*Incidence of Distant Metastases from Lingual Cancer Observed at the Memorial Hospital*

Total number of autopsies	67
Number showing distant metastases	12 (18%)
Lungs	7
Liver	4
Mediastinal nodes	4
Pericardium	4
Pleura	4
Diaphragm	2
Ribs and sternum	1
Humerus	1

ulcer of the tongue. Even though therapeutic tests may be subsequently indicated in the form of antisyphilitic therapy, sodium perborate mouth washes for Vincent's ulcers or extraction of teeth, there is no contra-indication to making immediate biopsy.

A survey of both the past and the present day literature will reveal that there is no uniformity of opinion in regard to the necessity and justification for biopsy in cases of cancer of the tongue. Spencer and Cade<sup>12d</sup> called attention to the fact that the common tendency to give the patient a chance by treating an undiagnosed lesion as benign in many instances gives the cancer, rather than the patient, a chance. They also made the rather equivocal statement that a biopsy specimen should be taken, provided that "it is not detrimental to the patient." One might ask what possible detriment to the patient could result from taking a biopsy specimen in comparison to the absolutely fatal consequences of an undiagnosed and untreated cancer of the tongue. What could be more detrimental than the misfortune of treating syphilis or tuberculosis by irradiation or excision of the tongue under a mistaken diagnosis of



cancer? Without biopsy, most tuberculous and gummatous lesions of the oral cavity would be treated as cancer in the average otherwise competent cancer clinic. There is no way to make cancer a safe disease, but probably the weakest and most futile gesture which can be made toward this end is the simple omission of a biopsy.

One biopsy with negative results does not necessarily disprove the presence of cancer. The more intelligently the tissue fragment is removed from the indurated edge of the ulcer, the more dependence can be placed on the histologic report. In any case, the ulcerated surface of a malignant ulcer may be covered by exuberant simple granulation tissue, and therefore, if the clinical appearance of the lesion so indicates, when a biopsy gives negative results the examination should be repeated at least once. A safe precept is: In the presence of a suspicious lesion, *always rule out cancer first*. This usually means the removal of a biopsy specimen.

A biopsy specimen from a fungating cancer of the tongue is usually best taken by a biting forceps, a fragment about 3 to 5 mm in diameter being removed. If the lesion is deeply infiltrating, with a depressed, firm center, a scalpel may be used to remove a small wedge of tissue of about the same diameter. A lesion at the base of the tongue often cannot be approached by direct vision, and the specimen is preferably removed by a curved specimen forceps guided by a throat mirror.

*Cervical Adenopathy*.—An essential finding in the diagnosis of cervical metastases is palpable enlargement of the lymph nodes. Without such enlargement, it must be assumed for all practical purposes, at least for purposes of record, that such metastasis has not as yet taken place. Even though present, enlargement of lymph nodes within the area of drainage of an infected cancer may be due to pyogenic infection only, and in such cases the cancer itself may not have spread beyond the borders of the primary lesion. It must also be realized that lymph nodes are not necessarily diseased or in any way abnormal simply because they are palpable.

About 30 per cent of all cancers of the base of the tongue in the clinic at the Memorial Hospital are referred because of cervical lymphadenopathy with the primary lesion undiscovered. Not infrequently cervical nodes have been excised for biopsy and the patients referred with a diagnosis of "cancer of the neck." In all cases in which the complaint is only of cervical lymphadenopathy, the oral cavity, the base of the tongue, the nasopharynx and the pharyngeal walls should be carefully examined for a primary lesion. It should be remembered that *most cervical adenopathies in the adult are malignant and probably metastatic from cancer primary in the oral cavity or the oral and nasal pharynxes*.

*Delay in Diagnosis*—Unfortunately, the physician whom the patient first consults is often responsible for a serious delay in diagnosis. The significance of such diagnostic errors is due not only to the frequency with which they occur but also to the fact that the patient, his fears quieted, may procrastinate unusually long before seeking a second opinion. The average time between the patient's first visit to a physician and a correct diagnosis was five months in the present series, a figure which agrees fairly well with reported averages.<sup>13a</sup> In over 10 per cent of cases, antisyphilitic treatment had been given for periods varying from two months to two years (average six months) under a mistaken diagnosis of gumma. In about 6 per cent of these instances, the physician had noted the primary lesion and had applied a topical remedy, usually cauterization by silver nitrate, with an average delay in correct diagnosis of three months. Curiously enough, cancer of the base of the tongue is often confused with chronic tonsillitis. In a period of four years at the Memorial Hospital, 8 patients were referred after tonsillectomy for the relief of symptoms undoubtedly caused by the presence of a bulky cancerous ulcer at the base of the tongue.

The members of the dental profession are also responsible for some delay in diagnosis. In about 5 per cent of our series the patients had first consulted a dentist and had had teeth extracted in the neighborhood of the tumor itself, believing that the lesion of the tongue was simply dental trauma. The probable nature of the disease was immediately recognized by the dentist in less than 10 per cent of these cases.

*Differential Diagnosis*—The diseases most apt to offer some difficulty in differential diagnosis are, in the order of their importance, syphilis, tuberculosis, papilloma, superficially ulcerated or fissured leukoplakia and simple granuloma (Vincent's angina, trauma, etc). Less common conditions sometimes confused with cancer of the tongue are glossitis rhombica mediana and muscle xanthoma. Such conditions as hemangioma, lymphangioma and papillary fibroma resemble cancer so little that they never should be confused with it.

*Syphilis*—For several reasons, syphilis is responsible for more delay and confusion in the diagnosis of lingual cancer than is any other condition. First, a great deal of stress has been placed on the diagnosis of syphilis in medical education. Second, gumma and lingual cancer present about the same clinical appearance (fig 7). Third, about one third of all patients with lingual cancer also have syphilis.

Since in medical education the fact is stressed that syphilis may manifest itself in a variety of forms, it is perhaps natural that the physician should assume syphilis to be the sole cause of a chronic ulcer when the

<sup>13a</sup> Rahausen, A. Cancer en la cavidad bucal, Santiago, Chile, Instituto nacional del radium, 1936. Lane-Clayton.<sup>2</sup>

Wassermann reaction is positive. This assumption leads to the most frequent and tragic errors in the diagnosis of lingual cancer. In our clinic, we find that prior to admission more than 10 per cent of patients with cancer of the tongue have received antisyphilitic treatment for an average period of six months before the physician finally has realized that syphilis alone was not responsible for the lesion. *In a case of chronic ulcer of the tongue, a positive Wassermann reaction does not disprove the presence of cancer*, since syphilis and cancer of the tongue coexist in about one third of all cases, as has already been mentioned. As a matter of fact, the presence of a positive Wassermann reaction strongly suggests that an associated chronic ulcer of the tongue is cancer rather than any other condition.

Since gumma of the tongue is so rare (the incidence is less than 1 per cent of that of cancer of the tongue), it seems illogical to employ the



Fig 7—Gumma of the tongue is a rare disease and may closely simulate cancer. The diagnosis should be made only after exclusion of cancer by repeated biopsies and the complete healing of the lesion within a month under antisyphilitic treatment. A lesion of the tongue which persists for more than that time under aggressive antisyphilitic treatment is not a gumma.

therapeutic test without first making a biopsy. It is certainly unwise to persist in the therapeutic test for longer than three weeks, for it has been our experience that a gummatous ulcer of the oral mucous membrane will invariably heal within that time under aggressive antisyphilitic therapy. The clinical appearance of long-standing syphilitic glossitis with leukoplakia is not markedly altered even by heavy and long-continued antisyphilitic therapy, and the therapeutic test is therefore of no value in these cases.

*Tuberculosis*—Tuberculous ulcers of the tongue are often confused with cancer and as such are referred to a cancer clinic. The relative frequencies of cancer, tuberculous ulcers and gumma of the tongue according to the admission records of the Memorial Hospital are respectively, about 100, 3 and less than 1. Tuberculous ulcers are usually

on the dorsum of the tongue but occasionally on the borders or at the tip. They ordinarily present a smoothly granular, yellowish, unhealthy base with little or no overgrowth of tissue, in contrast to the coarsely granular appearance of carcinoma (fig 8). Tuberculous ulcers are more apt to be painful and tender, with little or no induration. A diagnosis is made with the aid of biopsy (preferably repeated), a roentgenogram of the chest and examination of the sputum. Such lesions of the tongue or other oral mucous membranes are almost invariably secondary to demonstrable pulmonary tuberculosis. A correct diagnosis is especially important, since the proper treatment for cancer is almost the worst possible treatment for tuberculosis, and vice versa.



Fig 8—Tuberculous ulcers may occur on the borders, the tip or the dorsum of the tongue. They may closely simulate cancer in appearance but are usually both painful and tender. The diagnosis is made by biopsy, roentgen examination of the chest and examination of the sputum.

*Papilloma*—Any epithelium of the stratified squamous type may give rise to papilloma, and that of the tongue is no exception. Such lesions usually are the result of some form of chronic irritation to which the tissue response is a relatively benign overgrowth. In certain instances, papilloma may be an intermediary stage or a precancerous condition or may contain areas in which the transition is complete and true cancer is already present. Papilloma of the tongue most commonly occurs at the tip or on the borders. We have never seen it at the base. The lesions are usually papillary but may be either sessile or slightly pedunculated.

*Leukoplakia*—Leukoplakia is a common condition of the oral cavity. In a careful examination and analysis of 200 patients (100 men and 100

women) over 45 years of age without intraoral cancer at the Memorial Hospital, demonstrable leukoplakia was found in over 50 per cent of the men and in 10 per cent of the women. Leukoplakia so advanced as to be obvious on even casual examination may be found in about 15 per cent of otherwise normal men over 45 years of age.

Only the advanced fissured or verrucous types of leukoplakia offer any problem in differential diagnosis. In these lesions, cancer may be present at any point, and a decision as to the treatment may be somewhat difficult. Biopsy specimens should, of course, be taken from the most suspicious areas. If these are noncancerous, aggressive treatment for leukoplakia had best be carried out as a prophylaxis against cancer.

*Simple Granuloma*—A diagnosis of simple granuloma should never be made in the case of a chronic ulcer of the tongue without repeatedly negative results of biopsies and/or a prompt healing of the lesion under simple measures. The biopsy may be withheld temporarily if there is a history of competent and recent acute trauma, such as biting of the tongue, or if a painful tender ulcer, such as those present in herpes or Vincent's disease, suddenly appears. If such an ulcer persists longer than two weeks, a biopsy is definitely indicated.

*The Foliate Papillae*—These structures are situated on the edge of the tongue just opposite and anterior to its junction with the anterior tonsillar pillar (fig 1). The foliate papillae appear as variable but usually slight elevations in the surface contour, marked by several vertical fissures. Their color is ordinarily somewhat deeper red than the surrounding mucosa, and on a casual examination they may even resemble superficial ulcers. In cancerophobia, these areas are frequently noted, and with repeated examination and palpation by the patient the difference in color may become more marked. Therefore, in the differential diagnosis of cancer of the tongue in an apprehensive patient, these areas assume considerable significance. Lacassagne<sup>14</sup> and others have discussed this question in some detail. When cancer arises primarily in this area, its early stages may closely resemble a slightly inflamed foliate papilla.

*Glossitis Rhombica Mediana*—This condition is most often found in middle-aged men and consists of an indurated, nonulcerated, painless superficial ovoid or rhomboid mass situated in the midline of the dorsum of the tongue just anterior to the circumvallate papillae in the apex of the V. The appearance and especially the position are diagnostic. We have never seen cancer arise at this point in the tongue. No treatment is indicated for glossitis rhombica mediana except in the presence of

<sup>14</sup> Lacassagne, A. Radium Treatment of Cancer at the Curie Institute, Paris, New York: Thos. Nelson & Sons, 1931.

cancerophobia, in which the lesion may be surgically excised. A series of 11 cases has been reported from the Memorial Hospital.<sup>15</sup>

*Fibroma*—Papillary fibroma, a pedunculated smooth lesion usually 2 to 4 mm in diameter, commonly occurs at the tip of the tongue, apparently more often in females than in males. The benign character of this lesion is evident, and the treatment is by local excision.

*Angioma*—Hemangioma and lymphangioma should offer no difficulty in differential diagnosis at this time, but lymphangioma formerly was often mistaken for cancer of the tongue.

#### GENERAL PRINCIPLES IN THE TREATMENT OF CANCER OF THE TONGUE

There is considerable difference of opinion as to the most effective methods of treatment of cancer of the tongue. At one extreme are found those who advise surgical excision of the primary lesion (either by scalpel or by endothermy) and neck dissection for cervical metastases (Harmer,<sup>16</sup> Morrow,<sup>17</sup> New,<sup>18</sup> Truesdale,<sup>19</sup> Simmons<sup>20</sup> and others). Under this purely surgical management the operative mortality is high. Among various authors, the mortality is reported to be in the neighborhood of 25 per cent of the patients so treated. In their writings these authors either omit any specific mention of irradiation or concede its usefulness only in the treatment of recurrent or hopelessly advanced lesions, whereas in institutions where there are adequate facilities for irradiation and surgeons experienced in their application, there is a general agreement that irradiation, either alone or combined with conservative surgical treatment is the most applicable and generally useful method of treatment for the primary lesion (Berven,<sup>21</sup> Quick,<sup>22</sup> Roux-Berger,<sup>23</sup> Tailhefer,<sup>24</sup> Coutard,<sup>24</sup> and others).

15 Martin, H. E., and Howe, M. E. Glossitis Rhombica Mediana, *Ann. Surg.* **107** 39, 1938.

16 Harmer, W. D. Cancer of the Tongue, *Brit. J. Surg.* **15** 661, 1928.

17 Morrow, A. Cancer of the Tongue, *Ann. Surg.* **105** 418, 1937.

18 New, G. B. Cancer of the Tongue and Lower Jaw, *Tr. Am. Laryng., Rhin. & Otol. Soc.* **41** 1935, 1935.

19 Truesdale, P. E. Cancer of the Tongue, *Ann. Surg.* **78** 461, 1923.

20 Simmons, C. C. Treatment of Oral Cancer, *Am. J. Roentgenol.* **26** 5, 1931.

21 Berven, E. G. E. Resultats du traitement radiotherapique des cancers de la cavite buccale et du pharynx, *Gaz. med. de France (suppl. Radiol.)*, 1935 p. 377. Radiological Treatment of Malignant Tumours of the Oral Cavity and Pharynx, *Acta radiol.* **18** 16, 1937.

22 Roux-Berger, J. Cancer de la langue, *Bull. et mem. Soc. nat. d. chir.* **53** 1343, 1932.

23 Tailhefer, A. Traitement chirurgical des adenopathies du cancer de la langue. Resultats eloignes, *Mem. Acad. de chir.* **62** 975, 1936. Quick, loc. cit.

24 Coutard, H. Roentgen Therapy of Epitheliomas of Tonsillar Region, Hypopharynx and Larynx from 1920 to 1926, *Am. J. Roentgenol.* **28** 310, 1932.

There is also divergence of opinion regarding the treatment of the cervical metastases. Some investigators urge that surgical measures be used in all operable cases, irradiation being considered as a last resort<sup>25</sup>. Others recommend irradiation in certain instances and report cases in which irradiation alone resulted in permanent regression of the metastases<sup>26</sup>.

Whether surgical or radiation methods or combinations of the two are used for cancer of the tongue, these procedures are more difficult to apply and their complications are more serious in the tongue than in either the lip or the cheek. The local involvement of the tongue is seldom limited to the more accessible free portions of the tip and borders of this organ, which are fairly accessible to any method of treatment. Early in its course the disease tends to invade neighboring structures, such as the floor of the mouth or the tonsillar pillars, and such comparatively inaccessible and inoperable areas as the base or the deep extrinsic musculature of the tongue. In formulating a system of treatment for an unselected group of cases, one must therefore accept at the outset the fact that a relatively small proportion of all patients with cancer of the tongue may be considered operable when first seen. It follows, therefore, that surgery alone can never be the solution of this problem.

It is unfortunate that the current medical literature should still contain reports attempting to prove the superiority of one method alone—either radiation or surgical therapy—in the treatment of this disease. In our opinion, any such partisan attitude is entirely out of place in the management of so serious a problem as lingual cancer. At the Memorial

25 Cutler, M., and Buschke, J. F. *Cancer Its Diagnosis and Treatment*, Philadelphia, W. B. Saunders Company, 1938. Eggers, C. *Cancer Surgery Value of Radical Operations for Cancer After Lymphatic Drainage Area Has Become Involved*, *Ann Surg* **106** 668, 1937. Fischel, E. *Rational Therapy for Cancer of the Lower Lip*, *Am J Cancer* **15** 1321, 1931. Kennedy, R. H. *Epithelioma of the Lower Lip Suggested Routine for Treatment with Description of Operative Excision of Submental and Submaxillary Lymph Nodes*, *Ann Surg* **106** 577, 1937. Searby, H. *Treatment of Carcinoma of the Tongue*, *M J Australia* **2** 210, 1926. Wangensteen, O. H., and Randall, O. S. *Treatment and Results in Carcinoma of the Lip Report of One Hundred and Thirty Cases*, *Am J Roentgenol* **30** 75, 1933. Tailhefer<sup>23</sup>.

26 (a) Coutard, H. *Results and Methods of Treatment of Cancer by Radiation*, *Ann Surg* **106** 584, 1937. (b) Duffin, J. J. *Cervical Lymph Nodes in Intraoral Carcinoma Surgery or Irradiation?*, *Am J Roentgenol* **39** 767, 1938. (c) Lewis, F. O., in discussion of Symposium on Intraoral Cancer, *Am J Roentgenol* **26** 59, 1931. (d) Neill, W. Jr., in discussion of Symposium on Intraoral Cancer, *ibid* **26** 59, 1931. (e) Pfahler, G. E., in discussion of Symposium on Intraoral Cancer, *ibid* **26** 59, 1931. (f) Welch, C. E., and Nathan, I. T. *The Expectancy in Malignant Disease. II. Carcinoma of Lip, Oral Cavity, Throat, and Antrum*, *Am J Cancer* **31** 238, 1937.

Hospital our staff is composed of surgeons who administer or direct each detail of the treatment, whether by surgical intervention, radium or roentgen rays. The surgeon-radiologist, therefore, uses his unbiased judgment as to the nature and order of these several procedures.

In the treatment of cancer of the tongue, three distinct problems must be considered: (1) the hygienic care of the oral cavity before and during treatment, (2) the treatment of the primary lesion, and (3) the treatment of cervical metastases. Each of these problems must be dealt with by a separate and distinct set of procedures.

*General Hygienic Measures*—Before instituting treatment, prompt measures should be taken to improve the oral hygiene. The teeth should be cleaned by a dentist and the patient instructed in the use of a toothbrush. Sharp teeth, especially if in contact with the lesion, should be filed smooth or possibly extracted. If the treatment is to include heavy irradiation, however, it is often safer to leave the teeth in place, if possible, than to extract them, because of the danger of osteomyelitis—a complication which we shall presently discuss in more detail.

A normal hygienic condition of the oral cavity is maintained in great part by the constant flow of saliva. In many acute inflammatory disorders of the oral cavity and especially in those following irradiation, the amount of saliva is markedly decreased and the normal washing or flushing action of the saliva is lost. Therefore, the oral cavity should be irrigated frequently (every one or two hours) with copious mildly alkaline saline solutions (1 to 2 quarts of warm water with 1 teaspoon each of sodium bicarbonate and sodium chloride). Sodium perborate or zinc peroxide solution or other oxygenic mouth washes every two to four hours are also of great value during the radiation reaction and until the tongue has entirely healed. Daily visits to the clinic are advisable during the first few weeks of treatment. A successful result often depends to a considerable degree on a vigorous combating of oral sepsis, which is an important complication under any form of treatment.

The feeding problem may be one of the most important factors in successful treatment. It is sometimes undesirable for the patient to take food by mouth even though he is able to do so, because the limitation in movement of the inflamed tongue may induce a partial retention of the food in the mouth, where it tends to putrefy and increase the sepsis. For these reasons it is often advisable to administer most of the nutriment by nasal catheter during the period of the acute radiation reaction.

In all cases in which radiation reactions or open operative wounds are present in the mouth, vitamin therapy (especially B and C) and the administration of liver extract, either perorally or intramuscularly,



are of great value, since an inadequate intake of these substances will tend to produce lesions of the mucous membrane of the oral cavity

The question often arises as to whether the attendant syphilis, which commonly is first diagnosed at the same time as the cancer of the tongue, should be treated concurrently with the tumor. In our opinion, the presence of a positive Wassermann reaction with an uncomplicated noninfected cancer of the tongue does not call for antisyphilitic treatment in the beginning. If there is a great deal of glossitis and oral sepsis, it is probable that the attendant syphilis is responsible for at least a part of these complications, and in such instances marked improvement in oral hygiene may follow the administration of mild antisyphilitic treatment. Beyond this point antisyphilitic treatment should not be pushed until after the cancer is under control and healing has taken place.

TABLE 3—*Methods Used at the Memorial Hospital for Treatment of the Primary Lesion of Cancer of the Tongue*

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A	Radon seeds alone for very small early lesions
B	Fractionated peroral roentgen irradiation supplemented by radon seeds—the most useful method for all except the very small growths of the anterior two thirds of the tongue
C	Fractionated roentgen irradiation through the neck followed by supplementary radon seeds for cancer of the base of the tongue
D	Radon seeds (overdosage) followed in 5 to 10 days by partial glossectomy. This method is indicated only for a limited number of bulky fungating partly necrotic tumors
E	Variations in technic
1	Roentgen irradiation alone. This may be successful with a limited number of very radiosensitive tumors. Supplementary interstitial irradiation is probably indicated in all cases.
2	Low voltage lightly filtered peroral roentgen irradiation. This form of treatment should be limited to the very superficial growths on the anterior portion and dorsum of the tongue.
3	Surgical excision alone without either preliminary or postoperative irradiation. This procedure has a very small field of usefulness and should be limited to the fungating papillary tumors at the tip of the tongue.

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#### TREATMENT OF THE PRIMARY LESION IN CANCER OF THE TONGUE

In our opinion, the treatment of the primary lesion in the tongue should depend mainly on radiation, and if the lesion can be controlled by this means alone, the result most nearly approaches the ideal. Wide surgical excision would undoubtedly control a fair percentage of early accessible lesions, but this procedure is attended by marked functional disability and in any case is applicable only to the operable minority. It is probable that the majority opinion at this time favors irradiation rather than surgical treatment. A combination—irradiation followed by operation immediately or for late complications—is an indispensable method in certain instances. Since several techniques or combinations for the treatment of the primary lesion in cancer of the tongue are used in our clinic, each had best be described separately. These methods and their main indications are given in table 3.

*Radon Seed Implantation*—Gold radon seeds, in our opinion, are almost universally the best form of applicator for interstitial irradiation. In many clinics, radon or radium needles are considered superior to seeds (Berven,<sup>11</sup> Regaud,<sup>12</sup> Spencer and Cade,<sup>13</sup> and others). In most clinics where such opinions are held, radon seeds are not generally available or have never been extensively used, and we believe that where both are available the preference for seeds is rather uniform.

The surgeon who has become accustomed to the use of seeds and who then witnesses the introduction and suturing of needles into the tongue will be struck by the excessive trauma, which could be avoided, and the cruel necessity for maintaining these foreign bodies sutured into the tongue for eight or ten days, as compared to the rapid, painless introduction of seeds with use of local or short general anesthesia. In small superficial lesions (0.5 to 1.5 cm.) of the anterior two thirds of

TABLE 4—*Millicuries in Gold Seeds Required to Deliver Specified Doses to Masses of Various Diameters*

Masses of Various Diameters													
Skin Erythema Doses	Diameter of Mass, Centimeters												
	1 0	1 5	2 0	2 5	3 0	3 5	4 0	4 5	5 0	6 0	7 0	8 0	
	Number of Millicuries												
5	1 0	2 5	4 0	7 5	10	12	14	17	20	27	33	40	
6	1 2	3 0	4 8	9 0	12	14	17	20	24	32	41	50	
7	1 4	3 5	5 6	10	14	17	20	24	28	36	45	55	
8	1 6	4 0	6 4	12	16	19	23	27	32	43	53	65	
9	1 8	4 5	7 2	14	18	22	26	31	36	49	60	75	
10	2 0	5 0	8 0	15	20	24	29	34	40	54	70	90	
11	2 2	5 5	8 8	17	22	26	32	37	44	59	77	100	
12	2 4	6 0	9 6	18	24	29	35	41	48	65	84	110	

the tongue, seeds may be implanted directly into the growth from the mucosal surface with the region under local anesthesia. If the growth is larger or if there is a great deal of infection and tenderness, conduction anesthesia or general anesthesia may be indicated.

If radon seeds are used alone in a single application, the dose should be calculated so as to deliver about 10 threshold erythema doses to all parts of the tumor. The number of millicuries in seeds required to deliver specific tissue doses to masses of various sizes is given in table 4. So many factors enter into the selection of the interstitial dosage that this question must remain partly empiric. In the smaller tumors (requiring about 5 or 6 millicuries) it is sometimes most practical to implant a single dose of seeds. For the larger tumors the principle of protraction or division of the dose is of definite advantage. In this divided dose method, seeds are implanted every five to seven days in fractions of the dose. The total dosage of seeds in the latter technique must be increased by 25 to 50 per cent over that required in a single application. Total doses approaching or exceeding 20 millicuries destroyed in the tongue are apt to produce marked reactions and are

complications, and such heavy dosage should not be employed except by those who are experienced in this method of therapy

The surface of the tongue through which the seeds are implanted should be thoroughly dried first and then painted with tincture of iodine (fig 9). The introduction of infection during implantation or needling is one of the most potent factors in the production of subsequent radionecrosis. If the surface is recontaminated during implantation, it should be resterilized before proceeding. Ordinarily, seeds of 1.5 to 2.0 millicuries are the most suitable, but their individual strengths should depend somewhat on their number and distribution.

Even with the strictest sterile precautions, it is not always possible to avoid the introduction of infection when seeds are implanted directly through the oral mucous membrane. For the larger lesions of the middle third of the tongue and for all lesions at the base of the tongue the readily sterilized skin of the submental or suprahyoid region may

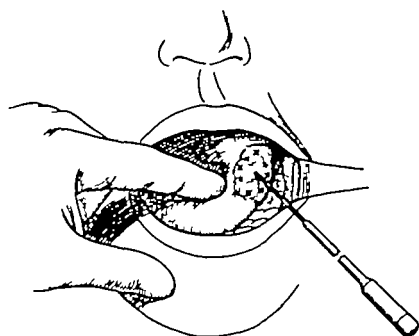


Fig 9—Implantation of radon seeds in cancer of the tongue

be used as the avenue of approach. The midline of the submental region from the symphysis to the hyoid contains no deep structures liable to injury by the implanting trocar needle. The skin at the point of the intended puncture is infiltrated with solution of procaine hydrochloride, and the needle is then slowly advanced through the deep tissues along its path up to the tumor. Through a stab wound in the skin, the implanting trocar needles are inserted and guided in their deep approach into the tumor by a palpating finger within the mouth (fig 10). After the implantation of larger doses of radon seeds (15 millicuries or more) into the tongue, protective shields may be constructed to spare adjacent normal structures from at least a portion of the unwanted effects of radiation."

*Fractionated Percutaneous Roentgen Radiation Supplemented by Radon Seeds*—This combination of radiation techniques is probably the most useful and practical method so far devised in the treatment of the pri-

27 Ackerman A J. Protective Shields in Radiation Therapy of Intraoral Cancer. *Am J Roentgenol* 38:746, 1937

mary lesion of cancer of the tongue. The value of the protracted or divided dose principle of roentgen irradiation for intraoral and pharyngeal cancer has been widely accepted, and no detailed discussion of its merits will be undertaken in this report. The main advantage of the fractionated over the massive dose principle is that with the former, the selective action of radiation is increased, so that a greater destructive effect is produced in the cancer with a lesser degree of harmful action on the normal tissues of the tumor bed. The main objection to the use of this principle in the treatment of cancer of the anterior two thirds of the tongue is that if the skin of the cheeks is used as the portal of entry the jaws and dental apparatus are so heavily irradiated that certain

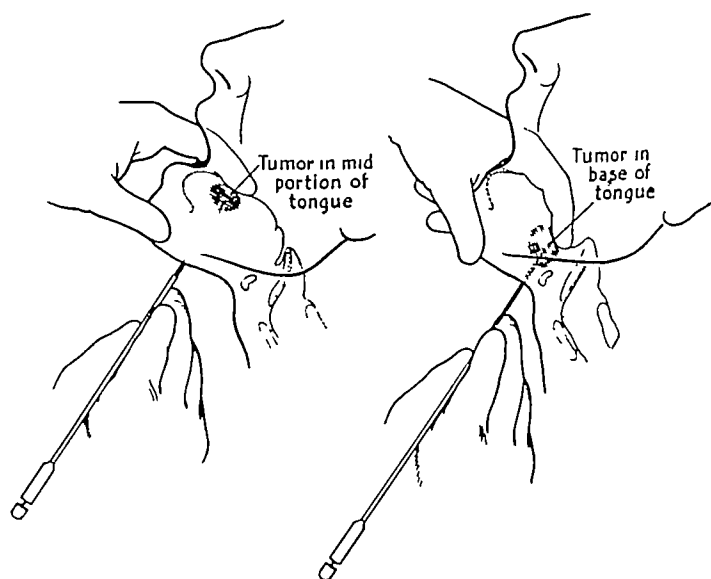


Fig 10—For interstitial implantation of tumors of the middle portion or of the base of the tongue, the introduction of infection may be avoided by inserting the implanting trocar through a stab wound in the skin of the submental or suprahyoid region.

late complications frequently ensue. This objection is almost entirely overcome if the open mouth is used as the portal of entry (fig 11).

An essential factor in peroral roentgen irradiation is the use of metal cylinders attached to the tube holder, which serve to separate the lips and jaws, to retract certain normal intraoral structures in the approach to the tumor, to limit the beam of radiation to the desired volume and area and to insure its correct direction to the lesion. For this purpose we have designed metal cylinders of various diameters (2.5, 3, 3.5, 4, 4.5 and 5 cm) and with the ends variously shaped. All are made to fit into a master cylinder in order to be readily interchangeable. A detailed description of this technic and the necessary apparatus has been published in a previous report.<sup>28</sup> For the average tumor in the middle

<sup>28</sup> Martin, H. E. Peroral X-Radiation in the Treatment of Intraoral Cancer, *Radiology* 28:527, 1937.

third of the lateral border of the tongue, the patient draws the tongue partly out and to one side, and the cylinder is brought down between the lips and the gums and centered directly over the tumor (fig 11). With daily treatments single doses of 300 to 400 r are given over a period of about three weeks for a total of 5,000 to 8,000 r, depending on the size of the portal, the thickness of the lesion and the dose of supplementary radon seeds. These factors of dosage must remain somewhat empiric and are selected for the individual case on the basis of past experience.

When a tumor on the tip of the tongue is irradiated, the tongue may be protruded from the mouth over a lead plate in which a notch has been cut to fit around the root of the tongue. The beam of roentgen



Fig 11—Lesions of the anterior two thirds of the tongue may be treated by roentgen radiation given through the open mouth. The patient protrudes and holds the tongue so that the lesion is properly positioned. Cylinders of various diameters are used to obtain the desired size of field. An electrically lighted periscope is used as a final check on the accuracy of the setup.

rays is then delivered to the tumor on the tip of the tongue obliquely downward and backward, and no normal tissues are irradiated except an unavoidable area through the notch into the root of the tongue. Either high or low voltage roentgen radiation may be used. If the depth of the tumor is several centimeters the more highly filtered roentgen radiation is advisable. Since the tumor is on the surface the target-skin distance should be reduced (30 to 35 cm) so as to intensify the superficial effect. The dosage is somewhat empiric and depends on the site of the portal and the intended size of the subsequent complementary dose of radon seeds.

*Radon Gold Seeds ("Overdosage") Followed in Five to Ten Days by Partial Glossectomy*—A combination of a massive dose of interstitial radiation followed within five to ten days by local removal of the tumor is a method formerly widely employed in our clinic for the treatment of many bulky lingual cancers. Its indications were based on the fact that many of these larger lesions, if irradiated by adequate doses of interstitial radon, were complicated by local radionecrosis and a long, painful convalescence. The local surgical removal was intended to eliminate the tissues condemned to subsequent radionecrosis. Since the more extended use of fractionated peroral roentgen radiation the incidence of radionecrosis from this cause has been markedly lessened, but partial glossectomy following radiation therapy is still an important technic, especially for the management of recurrences in heavily irradiated tissues.

When this combination of methods is employed, a dose of seeds is selected so as to deliver a desired number of millicuries destroyed within a specified time (five to ten days), after which the local tumor and contained radon are removed by actual cautery. The seeds are so placed in the tumor that they will certainly be removed with it. The dose is therefore termed an "overdosage", that is, it would be an overdose if the radon were left in place for its total period of decay. If the period between the implantation and cautery removal is short (seven to ten days), one may anticipate the effect of radiation therapy so that the operative procedure is accomplished before the local radiation reaction appears. The rate of decay of radon in from five to fifteen days is given in table 4.

*Technic of Glossectomy by Thermocautery*—In certain instances this procedure may be accomplished with local or conduction anesthesia, especially if the lesion lies in the anterior portion, or tip, of the tongue. If the lesion is more extensive or lies in the middle portion or extends to the base of the tongue, short chloroform anesthesia is to be preferred. After induction, the anesthesia is continued by a large nasal catheter inserted down as far as the tip of the epiglottis, and the pharynx proximal to the end of the tube is packed with gauze so as to close the surrounding airway and to prevent the aspiration of blood into the trachea. The tip of the tongue is transfixed by two sutures—one in the portion which is to remain and the other in the segment which is to be removed. The buccal, palatal and labial mucous membranes are next protected by heat-insulative shields (basswood splint-shaped to fit). The organ is then drawn out of the mouth and held by sutures. Excision is accomplished by the actual thermocautery which in our opinion is preferable to any form of endothermy. If the point of the cautery is kept red hot, the cutting is almost as rapid as with endothermy, and capillary oozing is practically nonexistent.

thermore, since deep coagulation is avoided the cut edges soon take on a healthy granular appearance, with more rapid healing. If the lateral half of the tongue is to be excised, a portion of the tip of the half which remains should be removed by an oblique incision (fig 12)

Assisted by traction on the transfixed sutures, the line of incision is kept under tension. After division of the free portion of the tip,

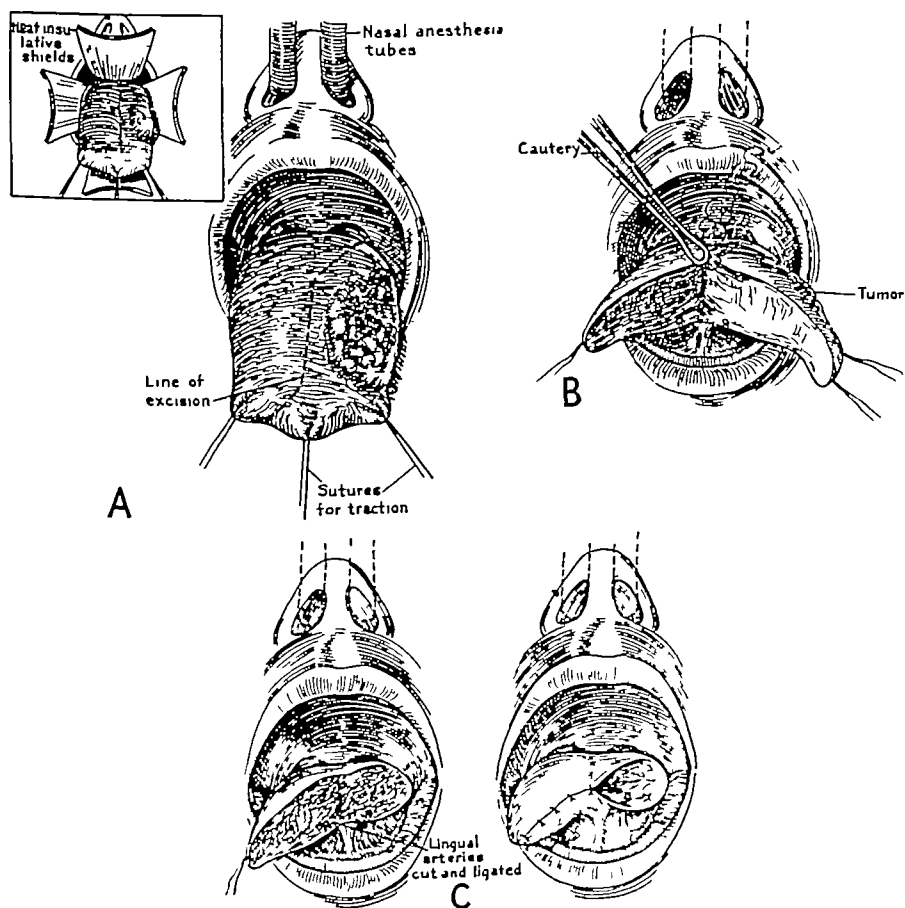


Fig 12—Partial glossectomy. *A*, the tongue is drawn out of the mouth and held by sutures. The cheeks and the mucous membrane of the lips are protected by heat-insulative shields of wood. *B*, with use of lateral traction the excision is accomplished by the red hot point of a thin bladed cautery. *C*, the cut ends of the lingual arteries are ligated, and the anterior portion of the wound is loosely closed by sutures.

traction is applied in an upward direction and a horizontal cut is made with the cautery in the floor of the mouth severing the genioglossus and hyoglossus muscles and proceeding backward into the intrinsic musculature, if necessary, to the valleculæ depending on the extent

and depth of the intended excision. The smaller arteries are clamped as they are cut. Suction rather than sponging is to be preferred to keep the operative field reasonably clear of blood as well as of smoke. Marked hemorrhage is not to be feared until one exposes the lingual artery, which enters the under surface of the muscular body of the tongue about opposite the first molar. As the incision progresses, the lingual artery is readily recognized as it appears in the depths of the wound, and at this point it may be grasped by a hemostat and severed. If it is severed without first being seen, the bleeding end is readily grasped by a hemostat and ligated.

The excision may extend backward into the valleculae if necessary, and by this cautery technic no particular difficulty is experienced from hemorrhage. Constant attention must be paid to the proper protection of the lips, cheeks, jaws and palate by heat-insulative shields, otherwise, a blistering of these mucous membrane surfaces may be caused both by contact and by radiant heat. The severed end of the lingual artery is always tied with a suture ligature, and it is usually necessary to tie three or four smaller bleeding points, but the total amount of blood lost should be small. The technic of ligation of these vessels will be described presently.

*Treatment of Cancer of the Base of the Tongue*—This anatomic form of the disease, in our opinion, should be considered inoperable in all cases, not only because of the comparative inaccessibility of this region but because of the highly malignant, rapidly growing, widely metastasizing and radiosensitive nature of these tumors. Cancer of the base of the tongue resembles pharyngeal cancer in many of its clinical features as well as in its favorable response to fractionated external roentgen irradiation. It is, however, neither necessary nor advisable to depend entirely on roentgen irradiation for these tumors, since the base of the tongue tolerates moderate doses of interstitial radiation without difficulty. A combination of external and interstitial irradiation is indicated in practically all such cases, in our opinion. The external irradiation is given first over a period of two to three weeks and followed immediately by supplementary use of radon seeds.

The protracted roentgen irradiation is usually given through the skin of the neck, since the open mouth cannot be satisfactorily employed as a portal of entry to irradiate the base of the tongue. The position of the exact center of the tumor is marked on the skin of the neck after careful inspection by a throat mirror and by digital palpation. With the jaws closed, the base of the tongue and the tumor will be found to lie a little below and anterior to the angle of the jaw. The location of the exact center of the portal will vary only about 2 cm. from the angle of the jaw, no matter what the size and position of the tumor at the base of the tongue, but these short distances are nevertheless of great importance.



In order to conserve the local and general tolerance, portals much larger than 7 to 8 cm in diameter should not be used unless indicated by the unusual size and extent of the tumor. Portals with a diameter less than 7 cm are difficult to localize and maintain in place over deep-seated tumors. For the average growth at the base of the tongue 2 to 4 cm in diameter, using two lateral portals of 7 cm diameter, one may administer a series of daily roentgen treatments of about 350 r to each side for a total dose of about 3,500 r times 2, and immediately on the completion of this roentgen irradiation insert a supplementary dose of radon seeds to deliver about 5 to 6 skin erythema doses (S E D) (table 4) into the tumor by the technic already described. The strength of the individual seeds should not be above 2 millicuries. If necessary, total doses of 16 to 20 millicuries properly distributed are well tolerated in this region after doses of protracted roentgen irradiation.

Since metastases from the base of the tongue most commonly occur first in the carotid bulb nodes, it is often possible by a slight tilting of the beam to include both these nodes and the primary lesion in the primary beam. The treatment of cervical nodes will be discussed further under a separate heading.

*Variations in Technic for Treatment of the Primary Lesion in Cancer of the Tongue*—Occasionally cancer of the tongue will be so radio-sensitive that the tumor may disappear early in the course of the peroral roentgen irradiation, and the regression later may become so complete that supplementary treatment by radon seeds may be justifiably omitted. However, in view of the increased safety and the slight disadvantage of a moderate dose of supplementary seeds, such attempts at the control of lingual cancer by external irradiation alone are not advisable, except in rare instances.

Low voltage, lightly filtered roentgen radiation (100 to 120 kilovolts, filter 1 to 2 mm aluminum) given perorally or to the protruded tongue may be used for very superficial but widespread lesions of the dorsum or of the anterior third of the tongue. The dosage employed is about the same as in the treatment of cancer of the skin. The method has certain disadvantages in that slight errors in technic, especially in exposing the lesion and in shielding the normal structures, are associated with troublesome complications.

As has been previously mentioned surgical excision alone is seldom indicated for the primary lesion of cancer of the tongue except possibly in those rare cases in which the tumor arises directly in the tip of the tongue and tends to fungate rather than to infiltrate. In these cases in which the lesions are not the most highly malignant amputation of the tip of the tongue with a margin of at least 7 to 10 mm of normal tissue is probably the most expeditious method.

## TREATMENT OF METASTASES FROM CANCER OF THE TONGUE

The management of cervical metastases is one of the major problems in the treatment of intraoral cancer, and the degree of success in dealing with this complication determines in great part the eventual prognosis. Over 60 per cent of unselected cancers of the tongue metastasize at some time during the course of the disease. Cancer of the tongue produces about 25 per cent of all cancerous cervical metastases. So far as the medical literature is concerned, most of the statistical reports on the treatment of cervical metastases have been based on series of cases of cancer of the lip, an anatomic form of the disease which is obviously not representative of the whole subject because of its lesser degree of malignancy.

For the treatment of cervical metastases, there are available the same methods as those used for the primary lesion, namely, irradiation and operation. It has been our experience that both of these methods are indispensable, and in a general consideration of the special indications for each we wish to avoid so far as is possible the appearance of any partisan preference for one or the other method. Each method may be specifically indicated in certain instances, and a combination of the two is required in a considerable percentage.

From the strictly surgical viewpoint, cancers are usually classified into "operable" and "inoperable" groups, and customarily no onus is attached to surgery for its failure to benefit the "inoperable group." From the standpoint of irradiation, however, there is no equivalent for the term "inoperable." Therefore, when the treatment is by irradiation or a combination of irradiation and surgical therapy results are calculated on the basis of all tumors treated, and classification into "inoperable" and "operable" groups is of little practical importance. The apparent percentage of cures calculated on operable cancer treated by surgical intervention alone cannot be fairly compared with the results in all cases of treatment by irradiation and/or surgical intervention.

*Limitations of Neck Dissection*—The time honored method for the management of cervical metastases is neck dissection, and this procedure still ranks high under certain limited conditions. In cases of lingual cancer we have found it to have a very narrow range of applicability for the following reasons. Thirty-five per cent of all cancers of the tongue present metastases on admission. The treatment of the primary lesion alone—either by irradiation or by a surgical procedure—is a major procedure accompanied by marked local complications from which complete recovery cannot be expected for a period of several weeks. Neck dissection is also a major surgical procedure with a definite mortality. We have always believed that aggressive treatment of the primary lesion (either by a surgical procedure or by irradiation) cannot be accompanied or immediately followed by such a procedure as neck

dissection without an undue risk of serious complications or immediate mortality. If, for this reason, the neck dissection is deferred until the primary lesion of the tongue is healed, it will in many cases be too late. We therefore feel that if metastases are present on the patient's admission to the hospital there can be little question as to the contraindications for neck dissection.

Should cervical metastases from cancer of the tongue occur immediately after the healing of the primary lesion and therefore early in the course of the disease, an analysis of the clinical course in a large series of cases will reveal that such metastases are very apt to be bilateral or soon to involve widely separated or outlying areas of the neck. Neck dissection in such instances would therefore probably have to be bilateral and extensive within a short period—a condition surely not favorable to a high percentage of cures. There are other factors, such as the advanced age and poor general condition of the patient, which constitute definite contraindications to neck dissection for lingual cancer.

*Limitations of Radiation Therapy for Cervical Metastases*—Radiation treatment likewise has certain definite contraindications. From the practical standpoint, one may consider problems of which the following example is representative. After treatment of early cancer of the tongue without metastases, there is prompt healing. The patient attends the follow-up clinic very irregularly but remains free of disease for two and one-half to three years, after which time he appears at the clinic with a fairly early, definitely palpable cervical metastasis on the same side as the primary lesion. Since little dependence may be placed on the regularity of his return over a long period for the multiple visits necessary to complete the irradiation of his cervical nodes, neck dissection would obviously be the best solution of the problem, because the procedure could be completed immediately without the risk of fatal neglect or noncooperation. Other contraindications to radiation therapy alone arise when cervical metastases from lingual cancer are large and bulky, with central necrosis and liquefaction. In certain of these cases the best solution of the problem lies in a neck dissection alone or in a combination of irradiation and surgical intervention. Specific indications for each particular method will be outlined under a description of technique.

*Prophylactic Treatment*—As the term is generally understood prophylactic treatment refers to those procedures applied to the neck for the control of possible metastases which are not palpable or otherwise demonstrable. Strictly speaking prophylaxis is not the proper term for this form of treatment since it is intended not to prevent metastases but to control impalpable metastases which may be present. Such treatment may be either surgical or radiologic.

In the management of intraoral cancer at the Memorial Hospital such prophylactic treatment to the neck either surgical or radiologic is not

employed for these several reasons. It will be conceded that if impalpable metastases are present in lymph nodes or elsewhere their treatment by irradiation or surgical intervention, to be effective, must be just as intensive as if the metastases were palpable and obviously present. As ordinarily advised and given, prophylactic irradiation consists of 1 to 2 skin erythema doses to both sides of the neck or other lymph node-bearing areas of the body. In our experience, such small doses as 1 to 2 skin erythema doses have never been observed (or at least reported) to sterilize a proved focus of epidermoid carcinoma or adenocarcinoma. Why, then, should such a dose be assumed to be capable of sterilizing an impalpable focus of cancer, the actual existence of which cannot be proved, simply because an individual patient survives and does not subsequently have metastases? The argument that by such irradiation any impalpable tumor cell may be partly devitalized is unacceptable, since partial devitalization of curable cancer is not sufficient. Cancer partly devitalized by irradiation to the point of partial necrosis may pursue just as malignant a course as untreated cancer.

The administration of cancer-lethal doses (5 to 8 skin erythema doses) to the entire potential node-bearing area of the neck would, in our opinion, be dangerous and unjustifiable, but this amount would be necessary to be of any possible benefit. Cancer-lethal doses, in order to be tolerated, must be limited to relatively small areas of the body. The actual volume and area occupied by curable palpable metastases are relatively small, and on this condition only may cancer-lethal doses be successfully given for palpable cancer in these areas. It is reasonable, therefore, to limit the application of radiation to cervical metastases according to this principle.

The greatest strength of the argument for prophylactic irradiation of the neck lies in the fact that its efficacy cannot be easily disproved. Reports of end results are frequently cited in support of its alleged benefits, but since the actual presence of the initial metastatic involvement remains extremely doubtful, the argument is purely negative and entirely unconvincing to the critical observer.

The lack of justification for any form of prophylactic treatment of the neck, especially radical neck dissection, can be further proved by statistical analyses. It is obvious that prophylactic treatment to the neck, even though efficacious, can be of no ultimate value unless the primary lesion is permanently controlled. Since this is true, it is highly significant that in our analysis of a series of 118 cases of cancer of the tongue limited by selection of those in which the patients were admitted without palpable nodes and in which the primary lesions were eventually permanently controlled, only 22 per cent of patients later had cervical metastases. In the final analysis, in only the latter 22 per cent would any form of treatment to the neck, prophylactic or otherwise, be of curative

value. It is also obvious that if prophylactic neck dissection had been performed in the whole group of 118 cases, they would have been of value in only 26 of these cases (1 in 5), while 92 useless operations would have been done (4 in 5), with a definite operative mortality. Under the higher reported mortality rates (10 per cent), about 12 of these patients would have died of postoperative complications. On the other hand, if neck dissections were omitted until nodes became palpable only one fifth as many operations would be necessary.

The practical application of these principles may be expressed by the following general rules for the management of cervical metastases:

1. If no palpable metastases are present, no treatment of any kind should be given.

2. If palpably and clinically involved nodes are present, one should limit treatment by irradiation to the individual nodes themselves, sparing

TABLE 5—*Methods Used at the Memorial Hospital for the Treatment of Cervical Metastases*

1	Protracted external irradiation through small portals followed by implantation of radon seeds. This method is the most generally useful for treatment of all cervical metastatic cancer.
2	Radical neck dissection. This method has a limited application but is very useful when indicated.
3	Radon seeds alone. This method is indicated only for very small or isolated nodes.
4	External irradiation alone. This method is useful only in very radiosensitive tumors.
5	Variations and combination methods: <ol style="list-style-type: none"> <li>Surgical exposure and implantation of radon seeds.</li> <li>Implantation of radon seeds in heavy dosage followed in 10 to 15 days by surgical excision.</li> <li>Surgical excision followed by radon seed implantation for an irremovable residuum.</li> </ol>

outlying clinically uninvolved areas and administering local radiation treatment to such outlying areas only if they later become involved.

3. If the treatment is to be neck dissection, the extent of this procedure is determined mainly by the anatomic form of the disease. Since neck dissection can be performed only once in a given area, it must therefore be complete within a given zone.

The methods available for the treatment of cervical metastases at the Memorial Hospital are outlined in table 5 in the order of their usefulness of application.

*Protracted External Irradiation Followed by Implantation of Radon Seeds (Method 1)*—This method is probably the most useful and the most generally applicable to cervical metastases from the various anatomic varieties of introral cancer. In general the purpose of this method is to confine the radiation to the immediate vicinity of the node in order to conserve as much as possible the integrity of the adjacent tumor bed and the general tolerance of the patient. External and inter-

stitial radiation are combined so as to derive the greatest possible benefit from a cumulation of their desirable effects. Their respective undesirable effects differ somewhat and are therefore not cumulative to the same degree. The main disadvantage of the method is that it is time consuming (three to four weeks) and, therefore, one of the simpler and less time-consuming methods may occasionally be preferable. Aspiration biopsy of the enlarged node should always be performed for purposes of record.

To localize the external irradiation, small circular portals (3 to 5 cm in diameter) are applied to each separate node, and depending on the size of the portal a total of 4,000 to 8,000 r or even more is given by daily divided doses over a period of two to three weeks. Immediately on the completion of this external dose, radon seeds in a tissue dose of 5 to 10 skin erythema doses (table 4) are implanted either through puncture wounds in the skin or after surgical exposure of the outer surface

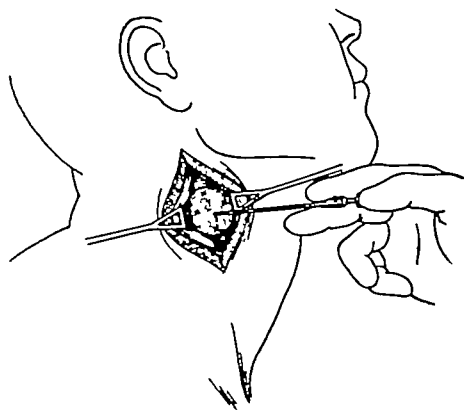


Fig. 13—Accuracy in implanting radon seeds in metastatic cervical nodes is favored by surgical exposure of the outer surface of the node.

of the node, in which case the cutaneous reaction to the roentgen rays is anticipated by performing the surgical exposure after about two weeks of irradiation. If the tissues are handled gently, an already blistered cutaneous surface may be painted with iodine and incised for exposure of the node, with prompt healing of the wound. With experience the surgical handling of irradiated tissues, either early or late, presents only moderate difficulty.

This conservative method of treatment, when applied only to the immediate area of the clinically cancerous node, makes possible its repetition in other areas should they be subsequently involved. Treatment of the necessary cancer-lethal intensity would not be tolerated if applied diffusely throughout the entire cervical region where metastasis might subsequently appear.

*Radical Neck Dissection (Method 2)*—The indications for radical dissection have already been discussed in some detail and will not be

repeated at this point, except to say that in cases of cancer of the tongue this procedure will be most useful if limited to those cases which conform to the following conditions

- 1 Metastatic cancer should be palpably demonstrable in the neck
- 2 The primary lesion should be healed and show no recurrence
- 3 The primary lesion should neither have involved nor crossed the midline
- 4 The metastases should be operable from the standpoint of their location and their mobility in the tumor bed
- 5 The metastases should be unilateral and on the same side as the primary lesion
- 6 The patient's general condition should be such as to withstand operation

The foregoing conditions under which neck dissection is permissible may seem rather rigid. However, it will be found, we believe, that few permanent cures of metastatic cancer of the tongue will be accomplished by neck dissection in cases which do not conform to the aforementioned conditions. If the case does not so conform, we believe that radiation methods offer a much greater chance of cure.

We favor local rather than general anesthesia in all cases of neck dissection, even though the patient may insist on general anesthesia. The highest mortality due to neck dissections (11 per cent) is reported from those clinics where general anesthesia is used as a routine procedure.

As compared to some other forms of intraoral cancer, the area of neck dissection for cancer of the tongue must be much more extensive. The operative area must extend from the midline of the neck (or beyond) to the anterior border of the trapezius muscle—from the inferior edge of the mandible and mastoid process to the clavicle.

The most useful types of incision, in our experience, are those illustrated in figure 14. Superficially, the plane of dissection should lie on the inner surface of the platysma myoides muscle and at about the same depth in the subcutaneous fat beyond the borders of this muscle. In superficial dissection the removal of the platysma myoides muscle probably does not increase the chance of cure since the presence of metastatic cancer in the superficial lymphatics occurs only by a retrograde spread relatively late when the disease ipso facto is incurable by operation.

In the course of the dissection all lymph node-bearing tissue between the platysma myoides muscle and the deep muscles is removed including the jugular vein, the sternomastoid and omohyoid muscles and the submaxillary salivary gland. No attempt is made to isolate the eleventh cranial nerve which is sacrificed. The tip of the parotid salivary gland is cut across.

In closing the wound it should be realized that a great number of lymphatics have been severed and that there will be profuse serous discharge for the first few days. Therefore, several soft rubber tube drains should be inserted.

*Implantation of Radon Seeds Alone (Method 3)*—This method of treatment may occasionally be indicated for isolated outlying small nodes or small nodes recurring after any form of treatment. In general this method should be reserved for the smaller masses in which a heavy

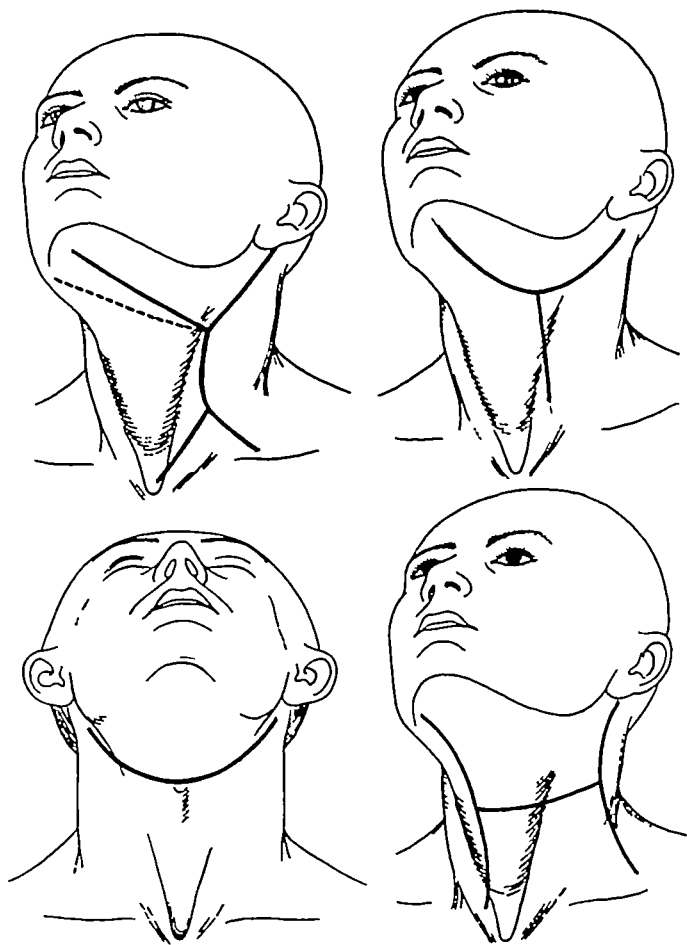


Fig 14—The most useful forms of incision for neck dissection

tissue dose may safely be given in a small volume by a moderate dose of radon seeds. The seeds may be inserted either through the skin or after surgical exposure. The dose depends on the size of the node and should be selected so as to deliver at least 10 skin erythema dose (table 4) or more throughout the mass. The proper geometric arrangement of the seeds is important, and the same rules should be followed as are described for the treatment of the primary lesion.

*External Irradiation Alone (Method 4)*—This method may be efficient for metastases from the more anaplastic and highly radioresistant



growths at the base of the tongue. It often happens that a metastasis in the upper deep cervical chain will lie directly superimposed over a primary lesion at the base of the tongue. Since treatment in such cases is always given first and mainly by external irradiation, the node will occasionally regress promptly and completely at the same time as the primary lesion under external irradiation alone, so that at the end of three to four weeks all evidence of the disease disappears. In these cases, one may occasionally feel justified in giving no other treatment. However, if the node regresses more slowly than the primary lesion or is palpable at the completion of the external irradiation, it is far safer to implant a supplementary dose of seeds, as in method 1.

*Variations in Procedure*—Surgical and radiologic procedures may be combined in several ways for cervical metastatic cancer, but we lack space to discuss them in detail here.

#### COMPLICATIONS

The complications following surgical procedures are apt to be acute and severe but of short duration, those following radiation treatment tend to be of lesser degree (at least in the beginning) but of longer duration.

*Pain*—The radiation reaction usually causes no particular discomfort when the tongue is at rest, but there is pain on movement, so that the patient tries to avoid any motion of the tongue, such as that necessary in the act of swallowing. A temporary increase in the salivary secretions and the seromucoid excretions from the tissues involved by the radiation reaction results in distressing salivation. For this complication, nothing gives greater relief than frequent mouth washes with compound solution of sodium borate (Dobell's solution) or copious irrigations of the mouth with a mild solution of sodium bicarbonate and saline solution. If a lesion with deep ulceration or radionecrosis is limited to one nerve distribution, such as the anterior third of the tongue and the adjacent floor of the mouth on one side only, neurolysis of the third division of the fifth cranial nerve by injection of alcohol may be indicated.

Since pain in cancer of the tongue is a symptom which will persist over a period of several weeks morphine is not suitable except when the prognosis is hopeless and the period of life expectancy does not exceed about two months. If the life expectancy exceeds this period to any great extent, one must take into account such factors as the increasing doses necessitated by addiction, the cost and the possible difficulty in obtaining and administering large quantities of the drug. A form of medication which we have found to be of most service is 10 grains (0.65 Gm.) of rectified acetic acid combined with  $\frac{1}{2}$  grain (0.03 Gm.)

of codeine, which the patient takes himself at six hour intervals, with the admonition that he is to use as little as possible

*Necrosis*—This complication, while frequent in all bulky irradiated surface cancers, is occasionally seen in the untreated advanced cancer of the tongue. It may also occur in early stages of the disease as a complication following irradiation, but is not due to the lethal effects of radiation alone. Unless infection is introduced, a completely devitalized area of cancer, deeply seated, will usually either be entirely eradicated by absorption or eventually resolve into a nonvascular calcified mass. However, if infection enters, the phenomenon known as radionecrosis accompanied by sloughing of the tissues invariably results. For all practical purposes, radionecrosis does not occur in the absence of infection.

Once initiated, the subsequent extent of this complication is determined by the intensity and extent of the tissue dose of radiation. Therefore, in order to localize the possible radionecrosis as well as other untoward effects of radiation a great deal of attention should be given to the principle of the most efficient manner of irradiation, including the geometric placement of the sources of interstitial radiation and the use of the smallest possible skin portals for external irradiation. Radionecrosis of limited extent may often be dealt with by local conservative measures, such as mouth washes, irrigations, sprays and the daily removal of slough, but in the case of persistent or widespread involvement convalescence is shortened by partial glossectomy, in which one removes the devitalized area with fair margins of viable tissue surrounding it.

*Hemorrhage*—This complication seldom occurs except in association with radionecrosis, although it may be caused from actual erosion by the tumor without necrosis. Although hemorrhage is by no means always fatal, in over 10 per cent of our unsuccessfully treated patients death was due to this cause. The blood supply of the tongue is mainly from the lingual artery, whose branches anastomose to some extent in the base of the tongue and in the tonsillar region with branches of the superior thyroid and facial arteries. The lingual artery enters the tongue medial to the hypoglossus muscle and runs forward deep on the under surface of the tongue as the linguae profunda artery. It is the latter branch which is usually responsible for the most severe hemorrhage in cancer of the tongue. The dorsal lingual branch ascends through the lingual substance to supply the base of the opposite side around the foramen caecum. With the exception of this anastomosis, and one at the tip of the tongue, the two lingual arteries do not have any marked communication across the midline of the tongue—a point of practical value in the control of hemorrhage. In surgical excision of radionecrosis, it will be found that severe or dangerous hemorrhage

dom occurs except from erosion of the linguae profunda artery. Hemorrhage from the base of the tongue is seldom profuse except when the erosion is deep enough to involve the main branch of the lingual or the facial artery. The lack of any elaborate anastomosis across the midline makes it unnecessary to ligate the arteries of both sides except when the necrosis or the operative procedure extends well across the midline.

Hemorrhage from an eroded lingual artery may be profuse, and death may occur from exsanguination within a few minutes. In the average case, however, the first hemorrhage is not apt to be fatal. In radionecrosis of the floor of the mouth, the spurting end of the vessel is not easily grasped directly, and tamponage is much more effective. A folded piece of gauze is pressed into the floor of the mouth and held by the finger. Immediate steps must be taken to clear the pharynx of blood, which may otherwise be aspirated and result in pulmonary complications.

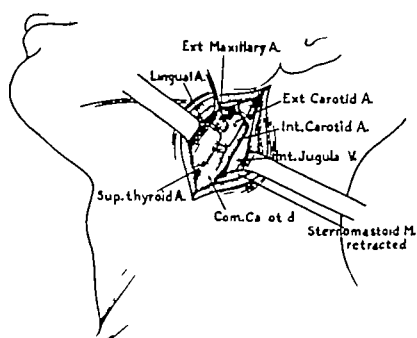


Fig 15—In hemorrhage from the tongue or the floor of the mouth, the lingual artery and usually the facial and external carotid arteries may be conveniently exposed and ligated by an incision along the upper anterior border of the sternomastoid muscle. It is advisable to cut the lingual artery between ligatures in all cases. The likelihood of recanalization is also reduced if ligatures of fine steel wire are used.

In all hemorrhages from cancer of the tongue, prompt ligation of the vessels of the neck is indicated.

*Technic of Arterial Ligation for Hemorrhage from the Tongue.*—The blood supply of the anterior portion of the tongue is derived from the lingual artery, with the addition of the tonsillar branch of the facial artery (external maxillary) which in part supplies the base. It is usually recommended in surgical texts that all of these vessels be approached by an incision through the submaxillary triangle, but we believe that they are best exposed for ligation at the bifurcation of the common carotid artery, which lies under the anterior edge of the sternomastoid muscle, a little below the level of the angle of the jaw. The latter approach gives the most direct access to these several branches as well as to the

external carotid artery itself, which should often also be ligated. We have described the technic of this operation in detail elsewhere. Should the hemorrhage originate from a centrally situated lesion, bilateral ligations may be performed, with an interval of five to ten days between operations if possible. The elaborate anastomosis of the terminal and deep branches of the thyroid plexus are such that no fear need be entertained for the vascular nutrition of the structures of the oral cavity or pharynx after these bilateral ligations of the external carotid artery.

*Sepsis*—This complication is inevitable in some degree in practically all cases of intraoral cancer under any method of treatment. Its significance in the early attempts at resection of the tongue was discussed at great length by Butlin, especially in the first edition of his "Diseases of the Tongue."<sup>4b</sup> The most useful measures for combating sepsis have already been described under the hygienic care of the mouth.

*Pulmonary Complications*—In the presence of advanced and complicated oral cancer, when the hypopharynx is examined with a mirror, a quantity of fluid, consisting of saliva, mucus and pus, will usually be found filling the piriform sinuses. Since swallowing is painful, the accumulated fluids tend to spill over into the larynx through the interarytenoid space and to be aspirated into the trachea. Bronchopneumonia (and, occasionally, pulmonary abscess) may result—the most frequently mentioned cause of death from the surgically treated lesions. The incidence of these, as well as of most other complications, may be greatly reduced by careful attention to the details of nursing care, especially with reference to oral hygiene.

*Osteomyelitis*—With all forms of intraoral cancer treated by massive doses of roentgen therapy, osteomyelitis is an occasional complication, and its inception depends largely on the diffuse irradiation of the bone after which any exposure of its surface, either by necrosis of the overlying tissues or by extraction of teeth, is apt to be followed by infection of the bone. Watson and Scarborough,<sup>29</sup> of our clinic, have described this complication in more detail in relation to intraoral cancer. Osteomyelitis developed in about 10 per cent of patients in our series with lingual cancer. If not exposed to infection from the outside, such avascular bone may remain and function without incident in the same manner as a dead bone graft or an ivory peg. However, this devitalized bone will behave as will any foreign body if infection is introduced—that is, an abscess is formed in this area and healing will take place only after sequestration and extrusion of the avascular bone.

There are several ways in which the incidence of osteomyelitis may be reduced. The first is by the use of peroral portals, such as the one which we have already described, to avoid diffuse and unnecessary irradiation.

<sup>29</sup> Watson, W. L., and Scarborough, J. E. Osteoradionecrosis in Intraoral Cancer, *Am J Roentgenol* 40: 524, 1938.

ation of the jaws. The second method is to avoid as much as possible the extraction of teeth at any time before, during or after local irradiation. The third is to make the interstitial doses as small and as effective as possible. With the firm conviction that the extraction of teeth is apt to be followed by serious complications in these cases, we use every reasonable alternative such as cutting off teeth at the gum level, killing the nerves and filling the root canals.

Once established, radio-osteomyelitis of the jaw should be treated conservatively, at least until the probable extent of the sequestration can be determined. The complication is less serious in the upper jaw than in the lower. In the latter, the arterial supply is from an end artery (inferior dental), and little assistance can be expected from anastomosis. In the upper jaw osteomyelitis tends to localize rather quickly, in the lower jaw it tends to be progressive. Partial resection of the mandible may be necessary in cases of aggravated lesions.

*Edema of the Hypopharynx and of the Glottis*—When in the late stages of lingual cancer a lesion at the base accompanied by widespread cervical metastases has been heavily treated with roentgen radiation through large portals, edema of the epiglottis and of the arytenoids frequently occurs, with concurrent dyspnea and dysphagia. The dysphagia may require the insertion of a nasal feeding catheter. The dyspnea may necessitate a tracheotomy, and in such a case, the incision should be as short and placed as low as possible.

#### PROGNOSIS

Except in the earliest stages, in which the tumor is small and situated on the edge of the anterior half of the tongue, the prognosis of cancer of the tongue is bad, and the only opportunity for cure lies in treatment by those especially trained. In the fatal cases in our series, the average duration of life from the first symptom to death was twelve months. Excluding immediate postoperative deaths, the duration varied between two months and seven years. Of all the unsuccessfully treated patients, 60 per cent died within one year after the beginning of treatment.

It will be noted in table 6 that the prognosis is best (47 per cent) under the age of 40 and that the cure rate progressively falls with advancing age to the poorest (19 per cent) over the age of 60. It should be realized, however, that our series does not necessarily represent the natural course of the disease but rather the clinical course under aggressive treatment.

Sex.—Our figures indicate that the chance of cure of cancer of the tongue in the female is almost 30 per cent better than in the male. The influence of sex on the prognosis of pharyngeal cancer treated by irradiation has already been noted by other observers. We believe that this

external carotid artery itself, which should often also be ligated. We have described the technic of this operation in detail elsewhere. Should the hemorrhage originate from a centrally situated lesion, bilateral ligations may be performed, with an interval of five to ten days between operations if possible. The elaborate anastomosis of the terminal and deep branches of the thyroid plexus are such that no fear need be entertained for the vascular nutrition of the structures of the oral cavity or pharynx after these bilateral ligations of the external carotid artery.

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better prognosis is due largely to the fact that cancer of any given histologic or anatomic form is generally more radiosensitive in the female than in the male

*Stage of the Disease*—In table 6 we have arbitrarily classified the lesions into three groups—"operable," "borderline" and "inoperable"—for the purpose of comparing our results and prognosis with other published statistics. In our clinic, such a classification has little influence

TABLE 6—*Factors Influencing the Five Year Cure Rate in 530\* Cases of Lingual Cancer Observed at the Memorial Hospital from 1927 to 1934*

	Total Number of Cases	Number of Five Year Cures	Per Cent of Five Year Cures
Age in years			
Below 40	32	15	47
41 to 50	87	29	33
51 to 60	186	42	23
Over 60	225	42	19
	530		
Sex			
Males	457	101	22
Females	73	23	31
	530		
Stage of disease			
'Operable'	141	80	57
'Borderline'	38	21	55
'Inoperable'	351	23	7
	530		
Metastases			
None at any time	191	85	45
None on admission	320	108	34
Developed after admission	129	23	18
Some time during course	339	39	11
Present on admission	210	16	8
	530		
Histopathologic structure			
Epidermoid carcinoma grade I	71	33	46
Epidermoid carcinoma grade II	318	64	20
Epidermoid carcinoma grade III	42	2	5
Adenocarcinoma	7	1	14
Transitional cell carcinoma	16	3	19
Lymphoepithelioma	3	1	33
Not classified	73	20	27
Associated leukoplakia	159	52	33
Associated syphilis	122	24	20

\* The discrepancy between this figure (530) and the grand total (556 cases) is due to the fact that in the earlier series (1927-1931) the calculations were made on the entire group, while in the second series (1931-1934) the "indeterminate cases" were excluded

in the selection of the treatment method, that is to say, the fact that a cancer is classified as "operable" does not signify that surgical treatment is the preferable method. In any case, such a classification must be rather arbitrary, since the opinions of individual clinicians must differ considerably.

The operability in the given case must be determined not only on the anatomic features of the primary lesion but on the operability of any cervical nodes and on the general condition of the patient. If radiation were not available, we believe that the tumors comprising the above mentioned operable group would be those selected for attempts at surgical cure in the average surgical clinic. Our five year cure rate in the



group treated by irradiation, surgical intervention or combinations of the two was 57 per cent, a figure which, so far as we have been able to determine, has not been equaled in any purely surgical statistics, even by the most careful selection of cases

The "inoperable" group includes all tumors of the base or posterior third of the tongue, all lesions which deeply invade the floor of the mouth and anterior tonsillar pillar and those with which it would be impossible to remove a margin of at least 1 to 1.5 cm of palpably uninvolved normal tissue. Patients with surgically inoperable cervical nodes, bilateral nodes on the side of the neck opposite the primary lesion, would also be included in this class, as well as those patients whose age and general condition would be contraindications to operation. The lesions which we have classified as inoperable and which make up 62 per cent of the total would probably not be mentioned, or at least not included in the calculation of end results, in any strictly surgical report. Our cure rate in this advanced group was only about 7 per cent. In interpreting the reasons for this low cure rate, it must be considered that the inoperable group includes all advanced and recurrent hopeless lesions, none of which has been excluded for this reason alone.

The "borderline" group is made up of those tumors in which the findings are not definite enough to permit of classification in either the frankly operable or the frankly inoperable group. The disposition of this group would depend largely on the courage and technical ability of the surgeon. The prudent surgeon would probably consider most of these tumors inoperable. Our cure rate in this small group, treated by a combination method, was 36 per cent, which is considerably better than the average for the whole. The mean cure rate in the whole series is determined to a considerable extent by the low cure rate in the inoperable group.

In Lane-Clayton's<sup>2</sup> compiled tables listing the postoperative survivals reported by various surgeons, there is included in each of the titles the phrase "all stages of the disease." The fallacy of such a heading is immediately apparent. Since all of the patients were treated surgically, the reports obviously cannot include all stages of the disease, but only the operable and therefore early lesions.

*Position of the Growth*—The chance of cure of a tumor at the base of the tongue is only about one third that of a lesion in the anterior portion. This relatively poor prognosis is due mainly to the fact that cancer of the base of the tongue is practically never diagnosed early. Another factor in prognosis is a higher percentage of anaplastic and histologically malignant growths at the base of the tongue than in the anterior two-thirds.

Little difference is found in the prognosis of tumors variously situated in the anterior two thirds of the tongue. The least malignant

variety of lingual cancer is that which arises directly at the tip to form a fungating, papillary, only slightly infiltrating growth which tends to metastasize rather late in the course of the disease, if at all. This relatively good prognosis is counterbalanced by the more malignant character of those lesions arising on the lateral edges or under surfaces of the anterior third of the tongue. Such growths tend to be highly malignant, to infiltrate the floor of the mouth and to metastasize early in the course of the disease. Growths of the middle third (the most frequent site) carry about an average prognosis. Lesions arising on the dorsum are usually associated with long-standing and widespread leukoplakia, and, although these lesions are not in themselves of the most malignant character, they tend to be multiple or successive, since the mucous membrane of the whole dorsum of the tongue has usually undergone marked precancerous changes.

*Metastases*—The significance of this complication in the prognosis depends to a great extent on whether the metastatic nodes are present on admission (8 per cent cure rate in our series) or whether they develop after admission (18 per cent cure rate—only a little less than the average for the whole group). As we have previously mentioned, the net cure rate for the whole group (25 per cent) is markedly influenced by the low cure rate (8 per cent) which is obtained in the advanced group with metastases on admission. In the group in which no metastases were present (either on admission or at any time during the course of the disease), the cure rate was 45 per cent. This high figure is obviously due to the fact that this group was not only early but also included the less malignant varieties of lingual cancer.

*Histopathologic Structure*—Different portions of a given neoplasm may show different histologic structures. For instance, we have frequently observed intraoral cancers in which the first biopsy showed an epidermoid or squamous carcinoma grade 1 while later biopsies of the same lesion or of a metastasis revealed a different histologic picture, that is, squamous carcinoma grade 2 or 3. Similarly, the first biopsy of an untreated lesion may show a highly anaplastic tumor, but after incomplete regression under heavy irradiation a second biopsy may show a low grade radioresistant tumor in the residuum. In general, the low grade tumors follow a more benign course than do the anaplastic growths. Wide departures from the expected clinical courses are frequently found, and too much reliance should not be placed on tumor grading in the individual case unless supported by other clinical findings.

#### END RESULTS

A survey of the literature for reported end results in the treatment of cancer of the tongue reveals very few data suitable for comparison.

We have found few based on unselected clinical material<sup>30</sup> The most common fault with reported end results in cases of cancer of the tongue lies in the fact that the percentage of cures has been calculated only from lesions operated on (operable tumors) This practice began when surgical treatment was the one method and when the percentage of operable patients applying for treatment was probably even smaller than it is at the present time Though permissible in the time of Butlin, this method is entirely inadequate today Inoperability of cancer is no longer synonymous with incurability, and the general mortality or curability of cancer or of any given disease cannot be calculated from the cure rates obtained in minority cases

It must be realized further that an indiscriminate collection of lingual cancers cannot be divided readily into two distinct clinical groups—the operable and the inoperable There must always be a large portion of borderline tumors, the exact classification of which would depend to a large extent on the experience and the courage of the individual surgeon We have attempted to survey all of the literature of the past twenty years on cancer of the tongue in order to obtain end result data for comparison Practically all of the reports give the end results only in highly selected groups, usually consisting of patients operated on We have considered suitable only those reports which were made on groups of cases which were unselected and in which the period of observation of the whole group was five years or more<sup>31</sup>

The standard form used in our clinic for reporting end results is set down in table 7 It should be noted that all patients, in any and all stages of the disease, are accepted for record and are included in our calculations if they are able and willing to return for such treatment, palliation or observation as we deem advisable No patient is excluded because of the advanced stage of the disease Invariably a small number of patients (1 to 3 per cent) disappear after only one or two visits, possibly to take treatment elsewhere These "clinic shoppers" and patients seen only once for purposes of consultation are not included in our end result calculations A second type of patient excluded from our calculations is the nonambulatory patient (also 1 to 2 per cent) who is unable for one reason or another to return for treatment or palliation

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30 Blair, Brown and Byars (Our Responsibility Toward Oral Cancer *Ann Surg* 106 568, 1937), after reviewing about 400 papers on cancer of the tongue, reported finding not a single one which gave satisfactory data for calculation of a true end result figure Curiously enough, they then fell into the same error themselves by reporting only end results in 40 cases in which they had operated, rather than in the whole group from which the 40 cases of operable growths were selected

31 Berven<sup>21</sup> Roux-Berger<sup>22</sup> Welch and Nathanson<sup>26f</sup>

Several biostatisticians whom we have consulted have agreed that if the untraced patients who are free from disease constitute less than 10 per cent of the total, they may fairly be classified as indeterminate for statistical purposes. Untraced patients who still had cancer when last seen should be counted as failures. These inconclusive cases, in which (1) the patients have died of other causes without recurrence and (2) the patients have been lost track of without recurrence, constitute the indeterminate group, which should properly be subtracted from the total before the net end result is calculated. Any calculation made without this subtraction is inaccurate and does not represent what may be accomplished in the treatment of a given disease.

TABLE 7—*Five Year End Results in Cases of Cancer of the Tongue Observed at the Memorial Hospital from 1927 to 1934*

This series consists of the cases of all patients with histologically proved cancer of the tongue, both early and advanced, admitted during the specified period. Only those patients are excluded who, for any reason, were unable to return for treatment, palliation and observation in the outpatient department, and those who were lost track of within the first month after no more than one or two visits ("clinic shoppers").

Total number of patients		556
Indeterminate group		
Dead as a result of other causes and without recurrence	33	
Lost track of without recurrence	5	
Total number of indeterminate results		38
Determinate group Total number minus those of indeterminate group		498
Failures		
Dead as a result of cancer	368	
Lost track of with disease (probably dead)	2	
Living with recurrence	4	
Total number of failures in treatment		374
Successful results Free from disease after five years or more		124
Five year end results Successful results divided by determinate group (124/498)		25%

Calculated by the foregoing standards, the end results in the Head and Neck Service at the Memorial Hospital in the treatment of cancer of the tongue from 1927 to 1934 are given in table 7.

#### SUMMARY AND CONCLUSIONS

A series of 556 consecutive unselected cases of cancer of the tongue have been subjected to intensive clinical analysis and report. The past and present day methods of the treatment of lingual cancer are discussed and a description is given of the methods now in use at the Memorial Hospital. The prognosis in this disease has been studied by the analysis of five year survival rates in various selected minority groups. A net five year cure rate of 25 per cent has been obtained on the group as a whole.

## PERFORATION AS A COMPLICATION OF GASTRIC CARCINOMA

MELVIN A. CASBERG, M.D.

Resident in Surgery, City Hospital

ST. LOUIS

Perusal of the medical literature impresses one with the infrequency of references to perforation as a complication of gastric carcinoma. However, admission to the hospital of 2 patients with acute gastric perforation within one week was considered to be of sufficient interest to warrant presentation of the cases, with a review of those observed in the St. Louis City Hospital during the past ten years. Perforated peptic ulcers of the stomach present a more familiar surgical emergency, occurring in approximately 15 per cent of cases.<sup>1</sup> Preoperatively, differentiation between the types of perforation may be difficult if not impossible, because little if any time is afforded the various differential procedures, such as analysis of the gastric contents and complete roentgen studies.

The most comprehensive of the reports in the recent literature is that of McNealy and Hedén,<sup>2</sup> who reviewed 133 cases of perforation of gastric carcinoma. The incidence of perforation in this series was 4 per cent. They classified the lesions into the classic and the obscure type, the former presenting the classic symptoms of sudden onset of pain and abdominal rigidity and the latter being more benign in its course, with no evidence of generalized peritonitis. Numerically the two groups were about equal.

Other reviews are those of Aird,<sup>3</sup> Allen<sup>4</sup> and Friedenwald and McGlannon.<sup>5</sup> Aird summarized the literature, presented a case from his own practice, 7 cases from the Royal Infirmary of Edinburgh, Scotland, and 71 cases from the literature and then concluded that either

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1 Da Costa, J. C. *Modern Surgery*, ed. 10, Philadelphia, W. B. Saunders Company, 1931, p. 885.

2 McNealy, R. W., and Hedén, R. F. *Perforation in Gastric Carcinoma*, Surg., Gynec. & Obst. **67** 818, 1938.

3 Aird, I. *Perforation of Carcinoma of the Stomach into the General Peritoneal Cavity*, Brit. J. Surg. **22** 545, 1935.

4 Allen, A. W. *Carcinoma of the Stomach with Perforation and Metastasis to the Liver, Regional Lymph Nodes and Pelvis*, New England J. Med. **214** 647, 1936.

5 Friedenwald, J., and McGlannon, A. *Perforation in Carcinoma of the Stomach*, Am. J. M. Sc. **157** 1, 1919.

the complication is most uncommon or it is improperly diagnosed. He divided the 79 lesions into four clinical types, the first two of which represent two thirds of the reported lesions and correspond with the classic type of McNealy and Hedin.

During the ten year period 1930 to 1939 inclusive, 247 patients with gastric carcinoma were admitted to the St. Louis City Hospital. This is probably a conservative estimate, for only those whose lesions were diagnosed by physical plus roentgen examination and treated by operation, with biopsy or autopsy, were included. A history and physical examination alone, however suggestive, were not considered to be sufficient evidence for a positive diagnosis. In this series there were 7 cases of acute perforation with the typical picture of acute peritonitis, proved by operation with biopsy and/or autopsy. Obscure cases of chronic or localized perforation were not included because of the difficulty of classification due to the wide variations in symptoms and findings. This means that acute perforation was encountered as a complication in 2.4 per cent of cases of gastric carcinoma.

The average age of the patients in the entire series was 63 years, whereas the average age of those whose lesions perforated was 51 years. Of the total number of patients admitted, 200 were men and 47 were women, a ratio of 4 to 1. All of the perforations occurred in men.

The history and physical findings were typical with all the lesions which were complicated by perforation—pain, commencing as a sudden epigastric crisis and later spreading over the entire abdomen and giving rise to exquisite tenderness, and the classic boardlike rigidity. Roentgenograms taken in 4 cases revealed the presence of free air under the diaphragmatic leaflets in 2. Simple closure of the gastric perforation was undertaken in 5 patients and only 1 of these lived to leave the hospital.

#### REPORT OF CASES

CASE 1—E. L., a 67 year old white man, entered the City Hospital on Aug. 28, 1939, complaining of severe epigastric pain which had commenced suddenly about nine hours prior to hospitalization. The pain, which had its onset shortly after the evening meal, was so severe that the patient had to be helped into bed. The pain did not radiate but remained in the epigastrium and about the umbilicus. There were no pains in the shoulders or in the scapulas. The patient vomited three times but noticed no bright red blood or "coffee ground" material in the vomitus. There was elicited a history of indigestion during the preceding five months, with a loss of 20 pounds (9.1 Kg.) in weight during the same period. The indigestion was described as a "stuffy" sensation in the epigastrium, coming on shortly after meals and relieved by baking soda. There was no history of melena. Up to five months previously the patient had been entirely free of any symptoms referable to the gastrointestinal system.

Examination revealed the patient to be rather slender somewhat emaciated and pale. He appeared to be in moderate shock. The temperature was 101.6 F, the pulse rate, 116, the respiratory rate, 32, and the blood pressure, 115 systolic and 68 diastolic. The abdomen was boardlike in its rigidity and did not move with respiration. There was rebound tenderness over the entire abdomen, most marked just superior to the umbilicus. It was impossible to palpate the intra-



Fig 1—Biopsy specimen taken from the border of the gastric perforation, revealing bundles of muscle tissue between which are seen islands of infiltrating cells. This cellular element is made up for the most part by lymphocytes, but among these are included nests of polyhedral epithelial cells. The nuclei of the latter cells are round, and the cytoplasm is quite clear. No attempt at differentiation is observed (Dr S. H. Gray, pathologist).

abdominal viscera because of the rigidity. Percussion failed to reveal hepatic tympany, and on auscultation there was no evidence of peristalsis. The heart and lungs were essentially normal. Scapular hyperesthesia could not be elicited.

A rectal examination revealed no gross abnormalities. The blood counts on admission were as follows: white cells, 7,000 per cubic millimeter, red cells, 3,780,000 per cubic millimeter, and hemoglobin, 80 per cent. The urine showed no sugar, but there was a trace of albumin. The Kahn reaction of the blood was negative. The value for blood sugar was 86 mg and that for nonprotein nitrogen 23 mg per hundred cubic centimeters. A plate of the abdomen with the patient sitting revealed the presence of free air under the left diaphragmatic leaflet.

A diagnosis of generalized peritonitis due to a ruptured gastric ulcer was made, and after adequate parenteral hydration the patient was subjected to an exploratory laparotomy. The abdomen was opened and explored through an upper right rectus muscle-splitting incision. About 1,000 cc of cloudy fluid was found free in the general peritoneal cavity, extending down as far as the pelvis. There was no fecal odor to this fluid, and a culture was later reported as sterile. The greater omentum covered part of the anterior surface of the stomach, and a large amount of fibrinoplastic exudate had collected about the gastric bed. A hard, woody mass about 11 cm in diameter involved the greater portion of the lesser curvature and a part of the anterior surface of the stomach. A perforation was observed through the anterior gastric wall, close to the lesser curvature, near the incisura angularis. Numerous hard, discrete preaortic lymph nodes were palpated, but no other metastasis could be determined. A biopsy specimen was removed from the border of the gastric mass. The gastric necrosis and induration prohibited closure of the perforation by purse string sutures, so a patch of greater omentum was sutured over the perforative site, the free peritoneal fluid aspirated and the abdomen closed in layers, with a rubber dam drain to the involved area. Postoperatively a continuous Wangenstein nasal suction apparatus was set up, and adequate fluids were administered parenterally. The patient's course became progressively worse, and he died on the fourth postoperative day. Despite strenuous efforts, permission for a postmortem examination was refused. Microscopic section of the biopsy specimen taken at operation confirmed the gross diagnosis of carcinoma (fig 1).

CASE 2—A P, a 51 year old white man, was admitted to the City Hospital on Sept 3, 1939, complaining of severe pain in the upper part of the abdomen, nausea and vomiting. The onset occurred about ten hours prior to entry and shortly after the evening meal. The pain was sudden and knifelike and was described as a "hit in the stomach" which "doubled up" the patient. There were no pains in the shoulders, and no fresh blood or "coffee ground" material was noted in the vomitus. He had never experienced pain of this type before but had been bothered by belching and indigestion for five months. Because of these ailments he attended a clinic in this city and was given frequent feedings of bland foods and some "powders." No roentgenograms were taken during this five month period. The patient stated that he had lost no weight, but this was not borne out by physical examination.

Examination revealed him to be slender and emaciated. He was obviously in acute distress, lying very still in bed and moaning rather loudly. Both hands were held over the upper part of the abdomen, and the examiner's attempts at palpation were warded off vigorously. The blood pressure was 100 systolic and 70 diastolic, the temperature was 98.8 F, the pulse rate was 80, and the respiratory rate was 24. The thorax was essentially normal, and no hyperesthesia of the scapular regions was noted. The abdomen was boardlike in its rigidity and was splinted during respiration. The point of maximum tenderness lay over the epigastrium, though there was a rather diffuse abdominal rebound tenderness.



Auscultation revealed no peristalsis, and owing to the abdominal rigidity no intra-abdominal viscera could be palpated. Rectal examination revealed tenderness high in the anterior region above the prostate. The laboratory data were as follows: The urine showed no sugar, albumin or acetone; the white cell count was 19,900 and the red cell count 4,250,000 per cubic millimeter of blood, the Kahn test gave a negative reaction, the value for blood sugar was 89 mg and that for



Fig 2—Microscopic section of a lymph node removed from the border of the greater gastric curvature, revealing sheets of invading epithelial cells. Though there is not a definite tendency to differentiation, certain of the epithelial islands appear to be arranged in acinar form.

nonprotein nitrogen 25 mg per hundred cubic centimeters. A plate of the abdomen with the patient sitting failed to reveal the presence of free air under either leaflet of the diaphragm.

A diagnosis of perforated peptic ulcer was made, and after parenteral hydration the patient was subjected to an exploratory laparotomy. The abdomen was explored through an upper right rectus muscle-retracting incision. There was a

considerable amount of free cloudy fluid throughout the peritoneal cavity, and a layer of fibrinoplastic exudate covering the anterior surfaces of the stomach and transverse colon was noted. Along the lesser curvature of the stomach in its inferior and anterior extent was a hard, irregular mass approximately 10 cm. in diameter. In the center of this mass was a round perforation about 1 cm. in diameter. Numerous discrete, hard lymph nodes were present in both the lesser and the greater omentum, close to the gastric borders. Several large, hard nodes were also palpated along the preaortic area. There was no gross evidence of metastasis to the liver. The free peritoneal fluid was aspirated and an omental flap sutured over the perforative site. Two lymph nodes were removed from the greater omentum for microscopic section. The abdomen was closed in layers, with a rubber dam drain to the involved gastric surface.

The postoperative course was essentially uneventful, and the patient was discharged on the fourteenth day. On October 13 he reentered the hospital because of advanced emaciation and anorexia and died four days later, six weeks after the operation. Permission for a postmortem examination was refused. The biopsy specimen was reported as metastatic carcinoma of a lymph node (fig 2).

#### COMMENT

In comparing the average age of all patients with gastric carcinoma with that of patients with carcinoma complicated by perforation there is a definite difference, the former falling in the sixth decade and the latter low in the fifth. The incidence of perforation in this series compares favorably with that in the much larger group reported by McNealy and Hedin.<sup>2</sup> It must be remembered that these authors, in giving a 4 per cent incidence, included both the classic and the obscure type, which were found to be approximately equal in incidence.

The 2 reported cases are interesting because of the close similarity in the histories, physical findings and operative descriptions. The lesions fall into the classic type with typical symptoms of generalized chemical peritonitis. The advanced stage of gastric involvement observed at operation would speak for a greater duration of the malignant process than is suggested by the relatively short (five month) period of symptoms. In a series of 168 cases of gastric carcinoma, Lahey<sup>6</sup> described a group of 53 lesions which were known to be in a fairly early stage, and of this number 32, or 60 per cent, had been producing symptoms for six months or less, while 21, or 35 per cent, had produced symptoms for six months or over. Lahey continued to state, however, that extensive malignant lesions of the stomach can occur with relatively few symptoms.

The differentiation of this condition from perforated peptic ulcer presents a real problem when the patients are first seen after perforation.

<sup>6</sup> Lahey, F. H. Cancer of the Stomach, *S. Clin. North America* 14: 1033, 1934.

has occurred. Known gastric malignant tumors, observed in the hospital or elsewhere, with which sudden acute abdominal emergencies develop lend themselves to more accurate diagnosis. The differential diagnosis depends not so much on the physical findings as on the past history. McNealy and Hedim concluded that a history of rapid loss of weight and indigestion occurring in a middle-aged man who has suffered little, if any, from previous dyspepsia, weakness and epigastric pain is given considerable weight in diagnosing malignant perforation.

Immediate exploratory laparotomy is the therapy of choice. Should shock complicate the picture, parenteral fluids, blood transfusions and other combative methods must be used in an effort to prepare the patient for an early operation. Once the gastric lesion has been recognized and explored, further surgical steps must depend on the extent of the process and the condition of the patient. Ideally, gastric malignant tumors should be resected, but in the great majority of cases the consensus is represented by the opinion of Dickinson,<sup>7</sup> who stated that the primary operation should be limited to closure of the perforation, resection being reserved for a later time, when the patient is better able to withstand it. It is interesting to note that of the lymph nodes, grossly identical as to palpation and color, removed from the greater curvature of the stomach in the second case only one showed malignant invasion on microscopic section. The other node revealed chronic inflammatory changes. This certainly emphasizes the importance of the site of removal of the biopsy specimen.

Technically, closure of a perforation due to a gastric cancer is more difficult than closure of one due to a peptic ulcer. The former is more friable and indurated and does not lend itself to repair with a purse string suture or to other methods used in closure of a simple peptic ulcer. The simplest procedure is to cover the perforative site with a flap of greater omentum "tacked down" with interrupted absorbable sutures. After aspiration of the spilled gastric contents from the peritoneal cavity a rubber dam drain should be introduced to the region of the perforation with exit through a stab wound in the upper part of the abdomen. Drainage of the peritoneal cavity for ruptured peptic ulcers is a question depending on the lapse of time since perforation, the amount of peritoneal soiling and the surgeon, however, in the case of gastric malignant tumors which perforate, drainage is the procedure of choice in view of the fact that the latter cannot be closed with as much assurance that there will be no further leakage.

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<sup>7</sup> Dickinson, A. M. Perforation of Carcinoma of the Stomach, *Surgery* 5: 544, 1939.

## SUMMARY AND CONCLUSIONS

In a series of 247 proved gastric carcinomas there were 7 complicated by acute perforation and generalized peritonitis

The average age of the patients in the entire group was 63 years, as compared with an average age of 51 years for the patients with perforation

Two personal cases of perforated gastric carcinoma are presented in detail

The differential diagnosis between gastric perforations due to carcinomas and those due to peptic ulcers is difficult if the patient is seen after perforation has occurred

The initial operation should be limited to simple closure of the gastric perforation

Biopsy specimens should be taken from all perforating gastric ulcers

# ISCHEMIC CONTRACTURE OF THE LOWER EXTREMITY

THOMAS HORWITZ, M D

PHILADELPHIA

The purpose of this communication is to report 2 cases of disabling deformities of the right lower extremity of eleven and fourteen years' duration respectively, presenting the following features (1) healed fractures of the femur, (2) massive induration of the muscles of the leg and foot associated with atrophy and loss of motor power below the knee, (3) vascular dysfunction in the involved lower extremity, (4) contractural deformities of the foot and toes, (5) roentgen evidence of extraosseous calcification of the leg, and (6) histologic evidence (in 1 case) of massive degeneration of muscle tissue with fibrous tissue replacement and extensive calcification. In these cases there was a pathologic state in the lower extremity identical with Volkmann's ischemic contracture of the upper extremity.

## REPORT OF CASES

**CASE 1**—A white man 39 years old had sustained a fracture of the midshaft of the right femur eleven years previously. The fracture had been reduced by skeletal traction through the lower end of the femur, and this had been followed by immobilization on a Thomas splint for six months. Immediately after his injury he had noted swelling and ecchymosis of the right leg, pain in the right heel and numbness and coldness of the right foot, without disturbance in the color of the extremity. Shortly afterward he had noted loss of motor power in the foot and toes, marked firmness of the muscles of the leg and deformity of the right foot. The deformity recurred after a lengthening of the achilles tendon two years later. Despite prolonged physical therapy and the application of corrective shoes, his disability on weight bearing persisted.

*Examination*—The right lower extremity presented a mild genu varum deformity with  $\frac{1}{2}$  inch (1.2 cm) shortening, talipes equinovarus associated with multiple hammer toes, atrophy of the leg and foot and marked induration of all the muscles below the knee, especially in the extensor and peroneal compartments (fig 1). A scar over the right heel represented the site of a healed pressure sore. Motion was normal in the knee but was almost entirely absent in the ankle and in the small joints of the right foot. Sensation was unimpaired, and there were no trophic changes. Reactions of degeneration were obtained in all the muscles below the knee. On the right side the femoral pulsation was easily palpable, but the popliteal, posterior tibial and dorsalis pedis pulses could not be obtained, all arterial pulses in the left lower extremity were normal. Oscillometric readings were diminished in the right lower extremity, but the cutaneous temperatures of the two feet were equal and normal.

*Laboratory Data*—Blood Count The value for hemoglobin was 85 per cent (Dare) There were 4,900,000 red blood cells and 8,900 white blood cells per cubic millimeter The differential count was normal

Urinalyses The voided specimens were consistently normal, the specific gravity varying between 1 009 and 1 018

Blood Chemistry The value for calcium was 9.2 mg and that for phosphorus 3.8 mg per hundred cubic centimeters The value for serum phosphatase was 49 Bodansky units The value for nonprotein nitrogen was 29 mg, that for uric acid 3.3 mg and that for cholesterol 167 mg per hundred cubic centimeters

The Wassermann and Kahn reactions of the blood were negative

*Roentgen Data*—Right Femur There was a healed fracture of the midshaft, with slight malunion (fig 2 B)

Right Fibula and Tibia The bony structures and their associated joints were normal There was extensive calcification of the soft structures on the anterolateral aspect, limited to approximately the middle three fifths of the leg and tending to be arranged in linear streaks lying in the longitudinal axis of the leg (fig 2 C)

Right Foot The bones and their joints were normal There were equinus and cavus deformities and multiple hammer toe contractures (fig 2 C)

*Operation and Course*—Subcutaneous tenotomies of the achilles tendon and of the flexor and extensor tendons of the toes, subcutaneous plantar fasciotomy and dorsal exostectomy (internal cuneiform bone) of the right foot were performed without the use of a tourniquet A biopsy was performed on the anterolateral aspect of the leg, about 6 inches (15 cm) below the knee. The muscle tissue (tibialis anticus and extensor digitorum longus) was found to be replaced by yellowish white scar tissue which sectioned with difficulty, owing to the presence of considerable quantities of calcareous material Plaster immobilization from the toes to the knee with the foot in corrected position was followed by physical therapy, massage and manipulation All wounds healed by primary intention. The patient was greatly benefited by this operation but is prepared for a more extensive procedure in the event of a recurrence

*Histologic Picture*—Microscopic sections of the biopsy specimen from the leg were stained with hematoxylin and eosin, Van Gieson's stain and Weigert's elastic tissue stain In a few areas scattered bundles of muscle fibers were still recognizable These had undergone granular and hyaline degeneration, with partial or complete disappearance of their nuclei and loss of longitudinal and transverse striations In the main, the muscle tissue was replaced by dense fibrous tissue containing scattered nuclei In some areas this fibrous tissue had become vascularized Interspersed among the bundles of collagenous fibers were small islands of finely granular calcific material (fig 3) In other regions, which were poorly vascularized, cellular detail was no longer recognizable, and there was considerable necrotic debris, which took the eosin stain deeply In such fields there were extensive areas of calcification (fig 4) There were no inflammatory cells and no areas of hemorrhage A few scattered large cells were filled with yellow pigment There was no evidence of osteoid tissue or of immature or adult bone formation

CASE 2—A white man 27 years old had sustained a transverse fracture of the right femur at the juncture of the middle and lower thirds of the shaft, with overriding and displacement of the fragments, fourteen years previously. An attempt at closed reduction followed by immobilization in plaster of paris had



Fig 1 (case 1) —Atrophy of the right leg with slight genu varum. There is an equinovarus deformity of the foot, with multiple hammer toes. The scar on the heel represents the site of a healed pressure sore.

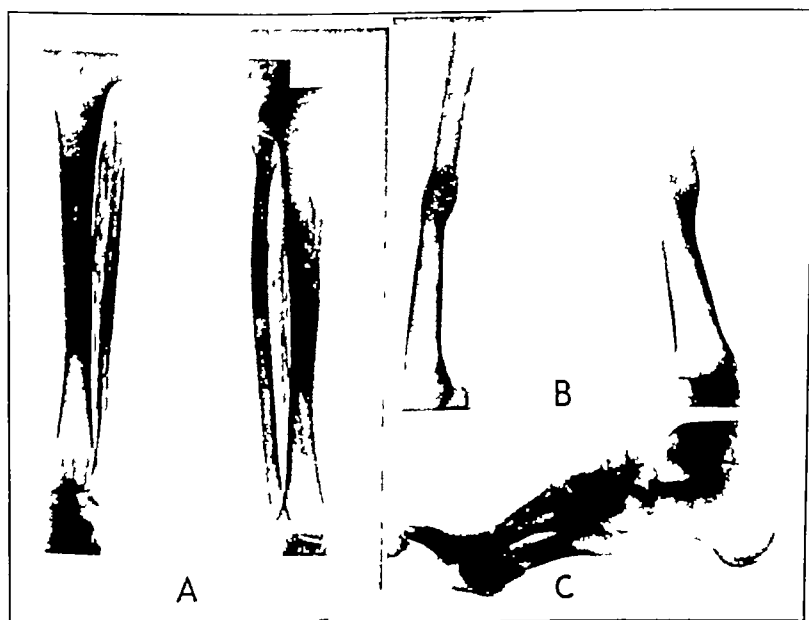


Fig 2 (case 1) —Roentgenogram of (A) the right tibia and fibula, showing extensive calcification of the soft tissues on the anterolateral aspect, which tends to be arranged as linear streaks in the longitudinal axis of the leg, (B) the right femur, showing a healed fracture of the midshaft with some malunion and (C) the right foot, illustrating the talipes equinovarus deformity with multiple hammer toe contractures.

been unsuccessful. Immediately thereafter the patient had experienced severe pain in his right leg distal to the fracture site, but he had noted no abnormal changes of color in the exposed toes. Two weeks later an open reduction had been performed under a tourniquet, and through a lateral incision the fragments had been fixed in good position by means of a steel ribbon band. The extremity was immobilized in plaster of paris. During the early postoperative period the patient experienced exquisite pain about the site of fracture despite the external fixation,

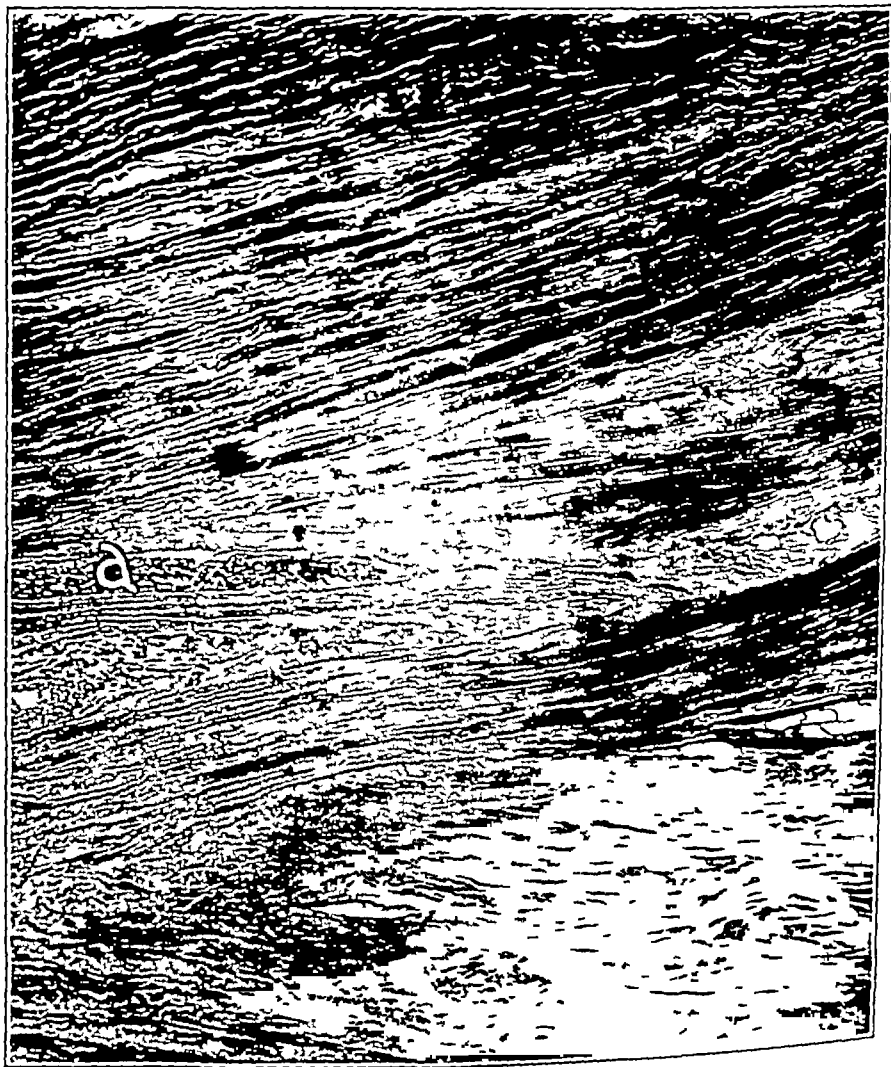


Fig 3 (case 1) —Histologic section of a biopsy specimen of muscle from the right leg ( $\times 50$ ). The muscle tissue is entirely replaced by dense fibrous tissue with scattered nuclei and occasional blood vessels. An island of finely granular calcific material has been deposited at *a*.

and he noted inability to move actively the toes of the right foot. When the external fixative device was removed at the end of three months, he noted that the leg was atrophied and the muscles of the leg remarkably firm, that he was unable to move the foot and toes and that the foot became cold and cyanotic when pendant. There gradually developed a fixed equinovarus deformity of the



foot with multiple hammer toe contractures, and these deformities recurred after subcutaneous tenotomies on two occasions. Because of this deformity he had experienced increasing pain and disability on weight bearing.

*Examination*—The patient walked with a limp on the right side due to a severe talipes equinovarus deformity with multiple hammer toes (fig 5). The two lower extremities were of equal length, and the right femur was solidly united. There were considerable atrophy of the right leg and a boardlike rigidity of all the

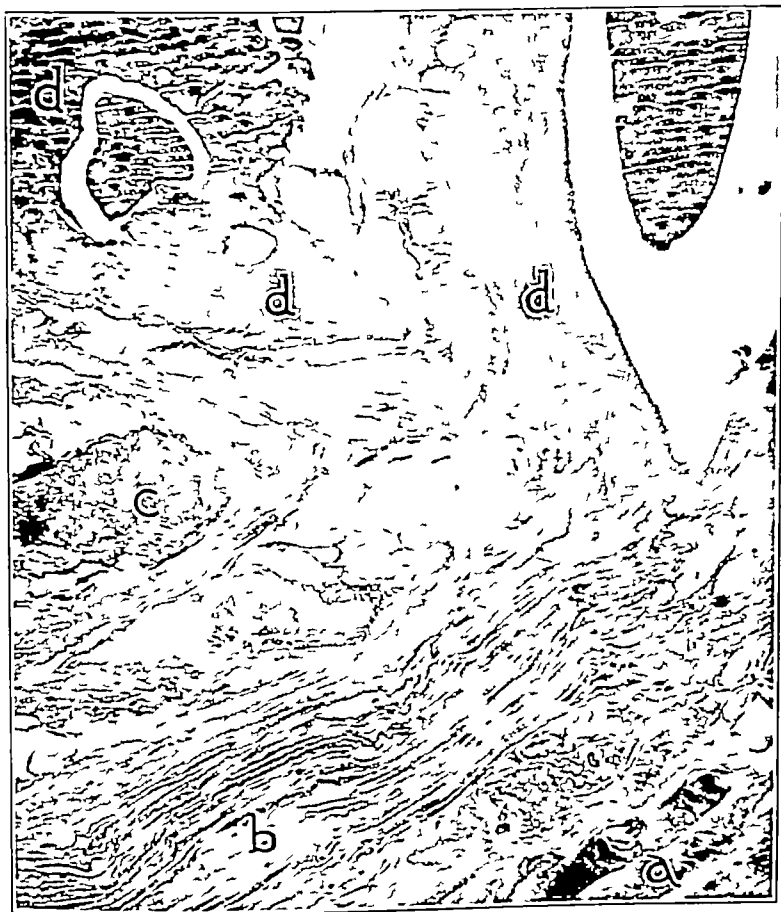


Fig 4—Another field from the same biopsy specimen ( $\times 50$ ). There is hyaline degeneration of muscle fibers (a), which are fragmented and which have lost their nuclei and striations. In the main, the muscle tissue has been replaced by dense fibrous tissue (b) containing few nuclear elements and some new vascular channels. In some areas there is evidence of extensive necrosis (c) with widespread calcification (d).

muscles below the knee. The overlying skin was normal and freely movable. Motion in the knee joint was normal, but there was no active or passive motion in the ankle joint or in the joints of the foot and toes. The right leg and foot became slightly cyanotic when the extremity was pendant, and the right foot per-

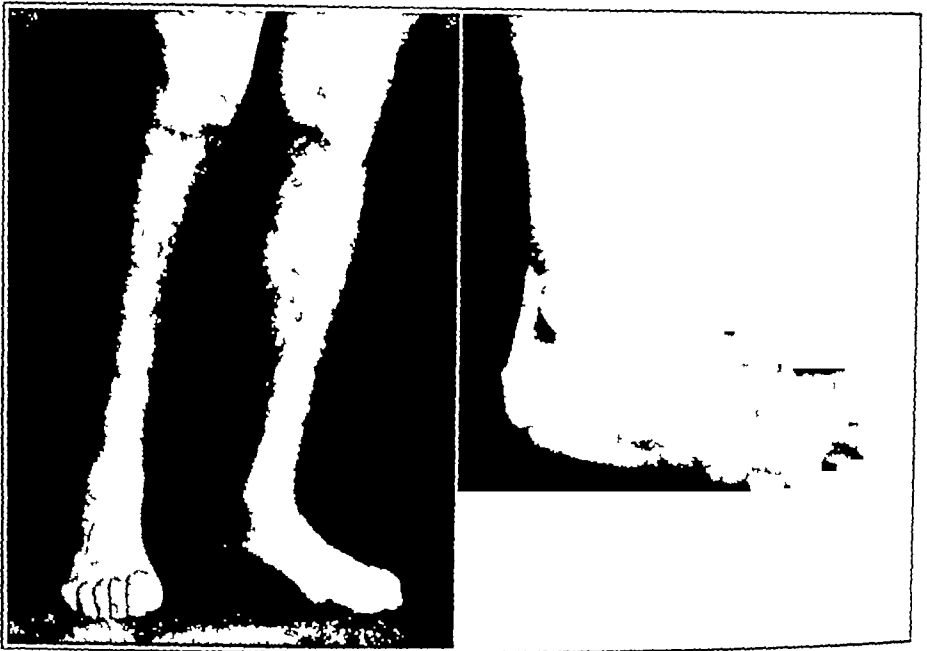


Fig 5 (case 2) —Atrophy of the right leg with an equinovarus deformity of the right foot and multiple hammer toe contractures. The dressings overlie two small ulcers produced by abnormal pressure on weight bearing.

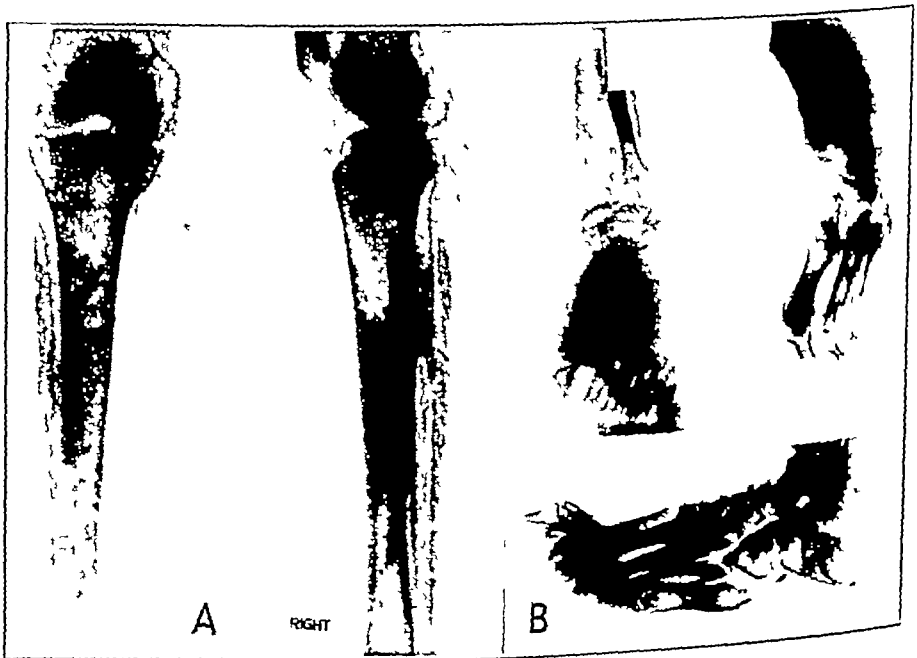


Fig 6 (case 2) —Roentgenograms of (A) the right tibia and fibula, showing extensive calcification of the soft tissues, which tends to be arranged in linear streaks in the longitudinal axis of the leg, and (B) the right foot and ankle. The axis of the ankle joint is directed outward. The foot presents an equinovarus deformity, with varus of the anterior and posterior portions of the foot and multiple hammer toe contractures. The fourth and fifth metatarsal bones are hypertrophied and deformed.

spired more freely than the left, but the cutaneous temperatures and oscillometric readings for both lower extremities were normal. The femoral, popliteal, posterior tibial and dorsalis pedis pulses were normal bilaterally. There were small superficial ulcers in the region of the heel and beneath the head of the fifth metatarsal bone, the sites of preternatural weight bearing.

*Laboratory Data*—The pertinent values for the blood and for the urine were normal.

*Roentgen Data*—Lower End of Right Femur, Right Tibia and Right Fibula. There was extensive calcification of the soft tissues in the anterior, lateral and posterior portions of the right leg, occupying approximately the middle three fifths of the leg and arranged as linear streaks lying in the longitudinal axis of the leg. Where bony structures were not obscured by soft tissue shadows, they were roentgenographically normal (fig 6a).

*Right Foot*. The fourth and fifth metatarsal bones were hypertrophied and deformed. (These bones had been the site of major weight bearing.) The remaining bones and their joints were normal. There were talipes equinovarus and multiple hammer toe contractures (fig 6b).

*Operation and Course*—Wedge resections were performed between the os calcis, astragalus, cuboid and navicular bones (triple fusion), and the hammer toes were corrected by multiple "flexor and extensor tenotomies," without the use of a tourniquet. A biopsy of the leg was not performed. Plaster of paris fixation from the toes to the knee was applied for three months until bony fusion was secured. A good anatomic and functional result was obtained.

#### LITERATURE

Previous reports and references have been tabulated in the accompanying table. It is not unlikely that the deformity in Cravener's<sup>1</sup> case was due to marked scarring incidental to repeated operative intervention and infection. The remarkable relief of pain and the disappearance of deformities of eighteen years' duration in Dieulafe's<sup>2</sup> case following periarterial sympathectomy suggest that this case may have been one of causalgia. The cases reported by Denuce<sup>3</sup> and by Riche, Aussiloux and Ginistie<sup>4</sup> presented atypical pictures of localized ischemic contractures involving the hamstring muscles, with resultant flexion deformities of the knee. In the second case reported by Jones and Cotton<sup>5</sup> no deformity developed, fasciotomy having been performed in the acute

1 Cravener, E. K. Volkmann's Contracture of the Leg, *New York State J Med* **32** 381-382, 1932.

2 Dieulafe, R. Syndrome de Volkmann du membre inferieur consecutif a la ligature de l'artere femorale. Guérison par sympathectomie peri-iliaque, *Bull et mem Soc nat de chir* **60** 473-474, 1934.

3 Denuce, M. Contracture ischémique, *Rev d'orthop* **20** 97-146, 1909.

4 Riche, V., Aussiloux, J., and Ginistie, J. Syndrome de Volkmann du membre inferieur, *Presse med* **47** 1173-1175, 1939.

5 Jones, S. G., and Cotton, F. J. Ischemic Paralysis of the Leg Simulating Volkmann's Contracture, *J Bone & Joint Surg* **17** 659-660, 1935.

# Summary of Twenty Cases of Ischemic Contracture of the Lower Extremity

Author	Year of Report	Patient's Sex	Patient's Age, Years	Lower Extremity	Possible Initiating Factors	Duration of Deformity	Physical Findings	Vascular Lesion	Nerve Lesion	Operation and Results
Volkmann, R. <i>Krankheiten der Becken- und Extremitäten</i> , in Pitha, F., and Billroth, Th. <i>Handbuch der allgemeinen und speziellen Chirurgie</i> , Stuttgart, Ferdinand Enke, 1872, vol. 2, pt. 2, pp. 234-240, cited by Franceschini	1872	Male	16	?	Hydrarthrosis of knee with flexion deformity, compression bandage	?	Talipes equinovarus (onset in less than one week)	None	None	None
Denoué <sup>2</sup>	1909	Male	15½	Left	Prolonged local exposure to low temperature (sitting on ice)	?	Flexion deformity of both knees, especially left, induration of hamstring muscles	None	None	Tenotomies of left hamstrings, good correction
Grig <sup>13</sup> (case 1)	1910	Male	9	Right	Contusion to leg with marked swelling and ecchymosis	1 year	Talipes equinovarus and multiple hammer toes, induration of calf, no active or passive motion in ankle and foot (deformity appeared 2 months after injury)	Dorsalis pedis and posterior tibial pulses not palpable	None	Tenotomies of Achilles tendon and flexor tendons, slight relief
Grice <sup>13</sup> (case 2)	1916	Male	62	Left	Ligation of femoral artery in Hunter's Canal for popliteal aneurysm	?	Talipes equinovarus, atrophy and induration of calf, no active or passive motion in ankle joint (onset 7 months after ligation)	Foot and leg cold and cyanotic, dorsalis pedis and posterior tibial pulses not palpable	Hypesthesia of leg and foot	Tenotomy of Achilles tendon and plantar fasciotomy, no relief
Bouquet <sup>18</sup>	1919	Male	21	Right	War wound on posterior surface of thigh in region of sciatic nerve, constricting bandage	1 year	Atrophy and "wooden" induration of calf, paralysis of extensor and peroneal muscles	Foot cold, diminished osseous measurements	Common peroneal nerve paralysis	None
de Ruffolo <i>Le paralisi ischemiche</i> , in Monografie dell'Istituto Rizzoli Bologna, S. Capelli, 1923, cited by Franceschini	1923	Male	23	Right	Fracture of right tibia at junction of upper and middle thirds constricting circular plaster bandage	?	Talipes equinovarus with multiple hammer toes skin dry and adherent to underlying tissue, limited active and passive motion of foot (onset 50 days after trauma)	None	None	Exploration

Meyerdine, 6 (case 1)	1930			Fracture of tibia and fibula	No data				
Meyerdine, (case 2)	1930			Fracture of tibia and fibula	No data				
Meyerdine, (case 3)	1930			Fracture of tibia and fibula	No data				
Cravener 1	1932	Male	41	Right Initial osteotomy of tibia and fibula for bowleg at 3 several reoperations	?	Atrophy of leg talipes equinovarus, limited motion of ankle and toes	None	None	None
Dieulafoy 2	1934	Mule	56	Right Ligation of femoral artery in Scarpa's triangle for war wound	18 years	Talipes equinus and hammer toes flexion deformity of knee atrophy of calf, exquisite pain in calf and heel	Diminished oscillometric readings	Areas of hypesthesia and anesthesia of leg	Right external iliac peroneal sympathectomy recovery
Jones and Cotton (case 1)	1935	Male	45	Right Severe crush injury of popliteal region	About 1 year	Talipes equinus, atrophy and induration of muscles below the knee	No pulses distal to groin, color changes in foot and diminished cutaneous temperature	Disturbed sensation recovery in 1 year	Tenotomy of Achilles tendon
Jones and Cotton 6 (case 2)	1935	Mule	46	Left Severe crush of popliteal region fracture of left fibula		No deformity	No pulsations distal to the groin, coldness and ischemia	Hypesthesia	Immediate fasciotomy (popliteal) complete recovery
Guyot J Villar J Chavannaz J and Courriades H Sur un cas de syndrome de Volkmann du membre inférieur gauche 1 de mnd de Bordeaux 11-1: 89 1935	1935	Male	47	Left Fracture internal tuberosity of tibia	Less than 1 month	Talipes equinus flexion deformity of knee in duration of calf muscles pain in leg and foot	None	Hypesthesia of dorsum of foot	None
Franceschelli N La retrazione ischemica di Volkmann dell'arto inferiore Ortop e traumatol dell'app mot 7 461-481 1935	1935	Male	28	Right Fracture tibia and fibula with delayed union and final mal union constricting plaster bandage	About 7 months	Talipes equinovarus with multiple hammer toes induration of calf muscles	Slight alternation in pressure and oscillometric readings	Hypesthesia of foot	None
Griffiths 11	1938	Mule	67	Left Embolism of femoral artery secondary to auricular fibrillation and thyrotoxicosis	1 month	Equinus deformity with multiple hammer toes induration of calf muscles (deformity appeared shortly after recovery of claudication)	Complete interruption of circulation, almost complete recovery 4 days after embolectomy (performed 17 1/2 hrs after onset) all peripheral pulses palpable except posterior tibial	None	Manipulation of foot and plaster fixation complete recovery

*Summary of Twenty Cases of Ischemic Contracture of the Lower Extremity—Continued*

Author	Year of Report	Patient's Sex	Patient's Age, Years	Lower Extremity	Possible Initiating Factors	Duration of Deformity	Physical Findings	Vascular Lesion	Nerve Lesion	Operation and Results
James, Bell <sup>19</sup>	1939	Male	53	Right	Fracture of tibia and fibula at juncture of middle and lower thirds, first plaster cast removed shortly after application because of pain and multiple wounds of the leg, fractures united in 4 months, second cast having been applied after healing of all wounds	3 years	Equinovarus deformity of foot and flexion deformities of all toes, induration of muscles of leg (deformity noted after removal of first plaster cast)	None	None	Amputation of toes, lengthening of achilles tendon and plantar fasciotomy, excellent functional and cosmetic result
	1939	Male	42	Right	Multiple injuries, including fracture of the pelvis and compound fracture of both bones of leg	5 months	Painful flexion deformity of knee, induration of hamstring muscles, nonunion of leg fracture, trophic ulcers of leg	None	None	Amputation
	1940	Male	39	Right	Fracture of femur in midshaft, contusion of leg with marked swelling and ecchymosis	11 years	Talipes equinovarus with multiple hammer toes, atrophy of leg and induration of leg muscles, little motion in ankle and foot joints	No pulsations distal to groin, diminished oscillometric readings	None	Multiple tenotomies of achilles tendon and toes and plantar fasciotomy, dorsal osteotomy good result
Horwitz (this paper)	1940	Male	27	Right	Fracture femur 6 inches (15 cm.) above knee, unsuccessful closed reduction, open reduction under tourniquet	14 years	Talipes equinovarus with multiple hammer toes, induration and atrophy of entire leg and foot superficial ulcers of heel and beneath 5th metatarsal head	Cyanosis of skin, normal peripheral pulses and oscillometric readings	None	Triple fusion and multiple tenotomies of toes good result

(prodromal) stage Meyerding<sup>6</sup> referred to 3 cases in which the condition followed fractures of the tibia and fibula but offered no details. The clinical features of the deformities of the lower extremity observed in my 2 cases were present, in whole or in part, in the remaining 10 cases.

## COMMENT

*Etiology*—It is generally accepted that the mechanogenesis of ischemic contracture is dependent in whole or in part on acute venous obstruction. This concept has been substantiated by the experimental evidence of Brooks<sup>7</sup> and of Middleton,<sup>8</sup> who produced a condition resembling ischemic contracture of muscle by sudden venous obstruction. Jepson<sup>9</sup> and Burman and Sutro<sup>10</sup> noted that venous stasis alone is not sufficient to produce such contractures permanently but that, in addition, proximal constriction of the soft tissues is necessary. Brooks, Johnson and Kirtley<sup>11</sup> and Wilson<sup>12</sup> noted the development of contractures in experimental animals after arterial ligation, which appeared later than those produced by acute venous obstruction and were attended by a less severe degree of inflammation. Clinical reports substantiate the concept that arterial obstruction may produce ischemic contractures in certain instances (Grieg,<sup>13</sup> case 2, Dieulafe,<sup>2</sup> Griffiths<sup>14</sup>). That arterial and venous interruption may occur concomitantly in the acute stage was demonstrated at operation by Jones and Cotton<sup>5</sup> in their second case.

The fundamental factors, therefore, are abnormal pressure conditions in a space containing muscles surrounded by resistant fascia and by

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6 Meyerding, H. W. Volkmann's Ischemic Contracture, *J. A. M. A.* **94** 394-400 (Feb. 8), 1930.

7 Brooks, B. Pathologic Changes in Muscle as a Result of Disturbances of Circulation. An Experimental Study of Volkmann's Ischemic Paralysis, *Arch. Surg.* **5** 188-216 (July) 1922.

8 Middleton, D. S. The Pathology of Congenital Torticollis, *Brit. J. Surg.* **18** 188-204, 1930.

9 Jepson, P. N. Ischemic Contracture. Experimental Study, *Ann. Surg.* **84** 785-795, 1926.

10 Burman, M. S., and Sutro, C. J. Experimental Ischemic Contracture, *Ann. Surg.* **100** 559, 1934.

11 Brooks, B., Johnson, G. S., and Kirtley, J. A. Simultaneous Vein Ligation. An Experimental Study of the Effect of Ligation of the Concomitant Vein on the Incidence of Gangrene Following Arterial Obstruction, *Surg. Gynec. & Obst.* **59** 496-499, 1934.

12 Wilson, W. C. Occlusion of the Main Artery and Main Vein of a Limb, *Brit. J. Surg.* **20** 393-411, 1932.

13 Grieg, D. M. Two Cases of Ischemic Contracture of Unusual Origin, *Clin. J.* **45** 361-363, 1916.

14 Griffiths, D. Arterial Embolism. A Study of Eight Cases, *Lancet* **2** 1339-1344, 1938.

bone and drained of blood by a peculiar anatomic arrangement which favors obstruction. The thin-walled veins collapse more readily than the heavier-walled arteries. Middleton<sup>8</sup> has discussed this mechanism in the upper extremity at the bend of the elbow, where a venous plexus with a diameter of about 2 cm, when compressed, will lead to obstruction of the venous drainage from the deep structures of almost the entire forearm. The comparative inextensibility of the aponeurotic compartments of the forearm may likewise embarrass venous return in the presence of hemorrhage and edema incidental to fractures of the forearm (Garber<sup>15</sup>).

The same susceptibility for venous interruption is noted in the closed fascial compartments of the popliteal space and of the leg. After dissection of the lower extremities of several human cadavers, I suggest the following sites for such susceptibility:

- 1 Where the popliteal vein lies posterolateral to the popliteal artery within the popliteal space, in juxtaposition to the posterior surface of the external femoral condyle. Compression at this level would interfere with the venous return from all the muscles of the leg and foot.

- 2 Where the popliteal vein lies ventral to the soleus muscle at the latter's origin from the prominent popliteal line. This would interrupt the venous return from all the muscles of the leg and foot except the medial and lateral heads of the gastrocnemius muscle.

- 3 Where the anterior tibial vein or veins perforate the interosseous membrane and pass between the two heads of the tibialis posticus or between this muscle and the fibula to join the posterior tibial vein or veins. This would interfere with venous drainage from the anterior and lateral muscle groups of the leg.

In a review of the literature, Hill and Brooks<sup>16</sup> collected 123 cases in which ischemic contracture had developed without previous application of a constricting bandage and 26 cases in which there had been no fracture. In the cases of involvement of the lower extremity collected in this article, a constricting bandage was the most likely factor in 1 case and might have been an influential factor in 4 more. In 3 cases there had been severe injuries to the soft tissues of the popliteal region or the calf, in 2 without fractures and in 1 with a simple fracture of the upper end of the fibula. In 7 cases there had been fractures of one or both bones of the leg, in 1 case a fracture of the femur at the juncture of its middle and lower thirds and in 1 case a fracture of the femur at its mid-shaft and a severe contusion to the calf.

15 Garber, J. N. Volkmann's Contracture as a Complication of Fractures of the Forearm and Elbow, *J. Bone & Joint Surg.* **21** 154-168, 1939.

16 Hill, R. L., and Brooks, B. Volkmann's Ischemic Contracture in Her-  
phila, *Ann. Surg.* **103** 444-449, 1936.



Peripheral nerve lesions are not considered important factors in the causation of this condition. They may complicate the clinical picture if the nerve has been injured at the time of initial trauma or if the nerve has become involved secondarily in scar tissue. Sensory lesions are not as a rule anatomically defined and are believed to be due to circulatory disturbances rather than to peripheral nerve lesions.

Leriche<sup>17</sup> and his followers consider injury to the sympathetic fibers in the arterial walls to be a greater factor than actual mechanical interference with the blood supply of the muscles. The good results reported by them as following periarterial sympathectomy and arteriectomy are difficult to explain in view of present anatomic knowledge and have been attributed by the antagonists of this theory to the coincidental fasciotomy. It would appear that surgical intervention on the sympathetic nervous system should be confined to those cases in which the condition is complicated by vasomotor instability or by causalgia.

The wisdom of fasciotomy during the acute (prodromal) stage, in the lower extremity as in the upper extremity, appears to be substantiated by the recovery and the avoidance of contractural deformities in the case reported by Jones and Cotton<sup>5</sup> after exposure of the popliteal space and evacuation of its extravascular bloody contents. If the dreaded contracture is to be avoided, pressure must be relieved immediately, as soon as the earliest evidence of impending vascular interference becomes recognizable.

*Clinical Picture*—The features of the acute stage in the lower extremity, as in the upper extremity, are pain, cyanosis, edema, paresthesias, hypesthesias, loss of motor power and trophic disturbances. In the residual stage the muscles become rigid and contracted. In the forearm this affects mainly the long flexor muscles of the fingers and thumb and the pronator muscles, and there result flexion deformities of the elbow, wrist and interphalangeal joints, with extension deformities of the metacarpophalangeal articulations and pronation contracture of the forearm. In the lower extremity, with involvement of the muscles below the knee an identical deformity is produced, with equinus at the ankle, cavus and varus of the foot and multiple hammer toe contractures. In the atypical cases in which ischemic contracture is limited to the hamstring muscles there are flexion contractures of the knee joint. In the stage of contracture, hypesthesia, trophic changes and evidences of vascular dysfunction (organic or vasomotor) may persist. Peripheral pulsations were not obtainable distal to the groin in 3 previously reported cases and in my first case. Intractable pain was a serious feature in 2

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17 Leriche, R. Retraction isolée des flechisseurs et des pronateurs apres fracture sus-condylienne de l'humerus et rupture seche de l'artere humerale. Arteri-ectomie. Guérison, Bull et mem Soc nat. de chir 54 212-216, 1928

reported cases, leading to amputation in 1 (Riche and his associates<sup>18</sup>), in the other it was relieved by periarterial sympathectomy (Dieulafoy). A definite nerve lesion (common peroneal nerve) complicated the ischemic contracture in 1 case (Souques<sup>18</sup>)

*Histologic Features*—The pathologic changes in the muscle during the acute stage are edema, infiltration of the interfibrillary spaces with leukocytes, disappearance of the nuclei of the sarcolemma, loss of muscle striations and granular and hyaline degeneration with atrophy and fragmentation of the muscle fibers. The pathologic features of the muscle in the stage of contracture are well exemplified in a biopsy specimen removed by me from the forearm of an 18 year old Negro with an ischemic contracture of the forearm and hand following a crush injury of the elbow region two years previously. Sections showed fragmentation and atrophy of the muscle bundles, with cloudy swelling and hydropic degeneration. The muscle nuclei stained poorly or had disappeared. In large areas the muscle tissue was replaced by dense, moderately vascular fibrous tissue in which were scattered islands of round cells and occasional large cells containing yellow pigment. In some areas there was calcification of the vessels, with necrosis. (Calcification of the soft tissues was evident on the roentgenogram.)

Histologic sections of the muscle from the lower extremity amputated by Riche, Aussiloux and Ginistié<sup>4</sup> showed areas of atrophy and swelling of the muscle fibers, with loss of striations and absence of inflammatory cells. Franceschelli<sup>19</sup> (1939) studied biopsy specimens from the tibialis anticus, triceps surae and plantar muscles of the involved leg of his patient, and these showed varying degrees of degeneration of the muscle fibers with proliferation of the interstitial connective tissue. There were no demonstrable changes in the achilles tendon or in the plantar fascia. The features of the biopsy specimen removed in my case represented a very advanced stage, there were massive replacement of degenerated muscle fibers by relatively avascular and acellular fibrous tissue and areas of extensive necrosis and calcification.

Such extraosseous calcification in the forearm and leg, representing the dystrophic form of pathologic calcification, is characterized by the deposit of lime salts in tissue of low viability or in dead tissue. Available evidence indicates that this process is associated with vascular deficiency and is dependent on such local factors as hydrogen ion concentration and carbon dioxide tension and that it is not related to general changes in calcium-phosphorus metabolism, to the state or amount of calcium

18 Souques, A. Un cas de maladie de Volkmann au membre inferieur, *Re. neurol* 35 451-453, 1919

19 Franceschelli, N. Retrazione ischemica dell'arto inferiore, *Arch di ortu* 55 348-357, 1939

and phosphorus in the circulating blood or to dysfunction of the parathyroid glands or of the kidneys (The laboratory data in my cases showed uniformly normal values )

#### SUMMARY AND CONCLUSIONS

Two cases of ischemic contracture involving the lower extremity are reported From these cases and a review of 18 previously reported cases the clinical, roentgen and pathologic features of this condition are defined Its occurrence must be anticipated after fracture or extensive injury to the soft tissues without fracture in the lower extremity, especially in the region of the knee and leg The stage of contracture and deformity may be avoided by fasciotomy during the acute (prodromal) stage Deformities of the lower extremity consequent on the contractures may be corrected by adequate nonoperative and operative measures

# FACTOR OF BILE STASIS IN EXPERIMENTAL PRODUCTION OF GALLSTONES IN DOGS

HANS G ARONSON, M D

CHICAGO

For the study of the origin of cholecystitis a method was devised which allowed introduction of material into the gallbladders of experimental animals (dogs) without causing appreciable damage to the wall of the gallbladder<sup>1</sup> This method consisted of leading a fine rubber catheter through an incision in the common duct into the cystic duct and into the gallbladder and, after withdrawal of the catheter, restoring a fairly normal flow of bile by inserting a glass cannula into the common duct The animals were killed after two to five days Absence of infection and dilatation of the biliary system was noted in a large number of control animals

In order to study the effect which long-standing cannulation might have on the biliary system, 3 of these dogs, together with 2 others, in which cholecystectomy was performed in addition to insertion of the cannula, were kept alive for a period ranging from sixteen months to two years When the animals were killed at the end of the observation period, precipitates were found in the cannula and in 1 instance in the gallbladder Though these precipitates could not be called stones in the proper sense of the word, there was sufficient resemblance to make description and discussion of these experiments worth while

Numerous attempts have been made by many authors to produce gallstones in the experimental animal, but none has ever been entirely successful Gilbert,<sup>2</sup> Gilbert and Fournier<sup>3</sup> and Mignot<sup>4</sup> infected the gallbladders of dogs, rabbits and guinea pigs with either *Bacillus typhosus* or *Bacillus coli* and produced concretions, Rosenow<sup>5</sup> obtained similar results, using streptococci in rabbits No description of these experiments, however, is given in any of the reports Richardson and Cushing<sup>6</sup> obtained stones by injecting *Bacillus typhosus* directly into

From the Department of Surgery of the University of Chicago

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1 Aronson, H G, and Andrews, E Proc Soc Exper Biol & Med **32** 1629, 1935

2 Gilbert, A Arch gen de med **10** 257, 1898

3 Gilbert, A, and Fournier, L Compt rend Soc de biol **4** 936, 1897

4 Mignot, R Arch gén de med **10** 129, 1898

5 Rosenow, E C J Infect. Dis **19** 527, 1916

6 Cushing, H Bull Johns Hopkins Hosp **1** 166, 1899

the gallbladder of the rabbit in only 1 instance Wilkie<sup>7</sup> produced a calcium precipitate in the gallbladder by ligation of the cystic duct and injection of anhemolytic streptococci into the gallbladder Phemister, Day and Hastings<sup>8</sup> produced calcium carbonate concretions by ligation of the cystic duct and injection of anhemolytic streptococci into the gallbladder

The colloidal chemical theory advocated by Aschhoff, Bacmeister, Shade and many others has found even less experimental support Reports on concretions produced by feeding experiments are scarce and inconsistent

Foreign bodies frequently become the nuclei of precipitation in bile Kretz<sup>9</sup> reported "stone formation" on thread left at operation in the gallbladders of rabbits and dogs This agrees with my own observation Whenever nonabsorbable suture material was used for closure of incisions in the gallbladder or in the common duct, the free ends of the sutures, which were in contact with bile, became coated with dark incrustations Rous and his co-workers<sup>10</sup> also obtained concretions in dogs which were due to the action of a foreign body They found precipitations resembling stones in the glass cannula inserted in the common duct and frequently in a long rubber tube attached to the cannula and leading to a collecting bag outside the abdomen Though these stones were never found "in the biliary system proper," the study is of great interest, since the authors excluded certain factors, such as activity of the gallbladder and infection Considering the length of the tubing used, it seems doubtful, however, that stasis of bile was absent in their experiments The concretions were carefully analyzed, and it was found that phosphorus and cholesterol were always absent, while carbonates were found in some and "much calcium" and pigment in most of them The pigment was described as showing the features of bilirubin-calcium as described by Städeler,<sup>11</sup> being insoluble in ether or chloroform and becoming soluble in chloroform after treatment with weak acid Because of this solubility behavior and the presence of much calcium in the residue, the authors concluded that originally bilirubin-calcium was present

#### I CANNULATION OF THE COMMON DUCT

*Method*—Insertion of the cannula was performed as follows

With ether anesthesia and strictly aseptic conditions, the abdomen of the dog was opened by a midline incision, and the common duct was incised longitudinally

7 Wilkie, A L Brit J Surg **15** 450, 1928

8 Phemister, D B , Day, L , and Hastings, A B Ann Surg **96** 595, 1932

9 Kretz, R, in Krehl, L, and Marchand, F Handbuch der allgemeinen Pathologie, Leipzig, S Hirzel, 1913, vol 2, pt 2, p 493

10 Rous, P, and McMaster, P D J Exper Med **37** 11, 1923

11 Städeler, G Ann d Chem **132** 323 1864

close to the duodenum. A soft French rubber catheter was introduced into the gallbladder, 10 to 15 cc of bile was aspirated by means of a syringe, and an equal amount of physiologic solution of sodium chloride was injected into the gallbladder. The catheter was then withdrawn, and a glass cannula was inserted and tied circular into the opening which had been made in the common duct.

In some instances the gallbladder was removed after cannulation of the duct.

#### PROTOCOLS

Dog 1—A cannula was implanted in the common duct. The observation covered fourteen months. The dog remained in good condition for about ten months, then became jaundiced and gained weight rapidly. It was electrocuted.

*Postmortem Study*—There was more than 5 gallons (20 liters) of watery, slightly bile-stained fluid in the abdomen. The gallbladder and the ducts were dilated, and the wall was thickened, on opening there were scar formation and a high degree of stenosis of the common duct where it had been opened. The cannula was not found in the body, consequently it must have passed by the bowel. There was a high degree of cholangitic cirrhosis of the liver.

Dog 2—The observation covered two years. The dog was in excellent condition throughout. There was no jaundice. The animal was electrocuted.

*Postmortem Study*—The choledochus was not stenosed. The ducts and gallbladder were not dilated and were free of deposits. The cannula was not found.

Dog 3—A cannula was implanted in the common duct. The observation covered sixteen months. The dog was in good shape, without jaundice. It was electrocuted.

*Postmortem Study*—There was slight dilatation of the gallbladder and of the ducts. There was thickening of the walls of the ducts, on opening there was some narrowing in the common duct where the cannula had been inserted. The cannula was not found. The gallbladder contained greenish bile, with two hard, somewhat friable concretions. The larger was 8.3 mm in diameter, the smaller, 2.2 mm. Analysis of the concretions revealed strongly positive reactions for cholesterol and calcium, a positive reaction for pigment, a trace of phosphorus, and a proportionately large amount of residue, unaccounted for.

Dog 4—Cholecystectomy and insertion of a cannula in the common duct were performed. The observation covered nineteen months. The dog was in good condition and not jaundiced. It was killed.

*Postmortem Study*—The ducts were slightly dilated. The cannula was found free in the common duct, with sutures around it which had cut through the duct. The cannula was covered with dark, hard incrustations on the inner and outer surfaces. The lumen of the cannula was somewhat narrowed but sufficiently patent to allow a fairly free flow of bile. Analysis of the incrustation revealed a trace of cholesterol, calcium, 11 per cent, a trace of pigment, and negative reactions for iron and phosphorus. There was a large amount of black residue, unaccounted for.

Dog 5—Cholecystectomy and insertion of a cannula in the common duct were performed. The observation covered nineteen months. The dog was in good condition and not jaundiced. It was killed.

*Postmortem Study*—The observations were practically the same as in dog 4. Analysis of incrustation revealed a trace of cholesterol, calcium, 0.5 per cent, and

trace of pigment, and negative reactions for iron and phosphorus. There was a large amount of black residue, unaccounted for.

#### COMMENT

One of 5 dogs in which a cannula was inserted into the common duct showed after sixteen months a cholangitic cirrhosis due to cicatricial stenosis of the common duct. The 4 other dogs remained in excellent



Fig 1 (dog 2)—The common duct was cannulated two years. The cannula was lost. The gallbladder and ducts, when opened, showed no dilatation. *A*, gallbladder, *B*, site of insertion of the cannula, *C*, duodenum.

condition, without clinical signs of biliary obstruction. When they were killed, from sixteen months to two years after operation, the duct system was found to be patent. In only 1 instance were there a slightly stenosing scar in the common duct and dilatation of the gallbladder (dog 3). The same dog also revealed two small hard stones in a grossly noninflamed gallbladder. On chemical examination these concretions were shown to contain cholesterol, calcium, some pigment, a trace of phosphorus and

unaccounted for residue. As gallstones have never been found to occur naturally in a dog's gallbladder, it seems that these stones were artificially produced. A likely cause for their formation is stasis. It is furthermore of interest that the cannula was found in place only in those dogs in which the gallbladder had been removed. The gallbladder therefore, acting as a "vis a tergo," was responsible for forcing the cannula out of the common duct. Analysis of the incrustations formed in the cannula



Fig 2 (dog 4)—Cholecystectomy and cannulation of the common duct for nineteen months were performed. The cannula, covered with incrustations, was lifted out of the duct. *A*, site where the gallbladder was removed, *B*, cannula, *C*, duodenum.

revealed in both cases small quantities of calcium and pigment and a comparatively large amount of a residue not accounted for. The only factors in the formation of these concretions appeared to be the slowing down of the flow of bile and the presence of the foreign body. The concretions were somewhat similar to stones found in the human bile duct system, in that both were low in cholesterol and calcium. A large



amount of residue is also found in most human gallstones. My recent studies seem to indicate that this residue constitutes polymerized bile pigment.<sup>12</sup> The slowing down of the flow of bile as well as the presence of the foreign surface appears to be responsible for the formation of these concretions, possibly by polymerizing the bile pigment. These concretions also resemble those produced by Rous in the cannula and rubber tube, though less pigment could be extracted in my experiments.



Fig 3 (dog 5)—Cholecystectomy and cannulation of the common duct were performed. The period was nineteen months. The cannula, covered with incrustations, was found loose in the common duct. *A*, site where the gallbladder was removed, *B*, cannula, *C*, duodenum.

## II. FACTOR OF STASIS IN PRECIPITATION OF BILE

In the previous study I was able to show that a cannula implanted and retained for a long period in the common duct of the dog became

<sup>12</sup> Aronson H G. A Component of Gallstones Insoluble in Ordinary Solvent and Accounting in Part for Their Dark Coloration. *Arch Path* 30:726 (Sept.) 1940.

coated with concretions on its inner and outer surfaces. In these experiments the gallbladder had been removed, and it was obvious that the elimination of expulsive action from the ducts produced by contraction of the gallbladder had played a part in the formation of these concretions.

In 1 dog two small stones had formed in the gallbladder, which was somewhat dilated secondary to implantation of a cannula followed by expulsion and partial obstruction (cicatrizization) of the common duct.

In order to analyze further the effect local stasis might have on precipitation of bile, the following experiments were carried out.

*Method*—A glass cannula with a bulb arising from one side of its middle was inserted in the common duct, and the bulb was wrapped in omentum. The size of the bulb varied from  $\frac{1}{3}$  inch by 3 inches (0.8 by 7.6 cm) to  $2\frac{1}{2}$  by 3 inches (6.2 by 7.6 cm), and the neck between the bulb and the cannula was  $\frac{1}{3}$  inch (0.8 cm) in diameter. This opening was large enough to allow free flow of bile from the duct into the bulb. It is obvious that bile in the bulb would be somewhat stagnant.

#### PROTOCOLS

Dog 6—A cannula with a bulb ( $1\frac{1}{2}$  by 2 inches [3.2 by 5 cm]) was inserted. The observation covered sixty days. The dog was losing weight but was not jaundiced. It was killed.

*Postmortem Study*—The bulb was filled with light green bile and dark sediment. The ducts and gallbladder were dilated. The ducts contained green bile, the gallbladder, dark brown bile. No obstruction was found in the ducts. Analysis of bile from the gallbladder revealed a value for pigment of 150 mg and a value for calcium of 47 mg per hundred cubic centimeters. Bile from the ducts contained 75 mg of pigment and 33 mg of calcium per hundred cubic centimeters. Bile from the bulb contained 135 mg of pigment and 15 mg of calcium per hundred cubic centimeters.

Dog 7—A cannula with a bulb ( $2\frac{1}{2}$  by 3 inches [3.2 by 5 cm]) was inserted. The observations covered ten days. The dog died.

*Postmortem Study*—There was peritonitis, with bile-stained fluid, there was no visible perforation. The bulb was filled with thin green bile. There was a small black precipitate on the inside of the neck, where the bulb connected with the cannula. Chemical analysis of the precipitate revealed a negative reaction for cholesterol, positive reactions for pigment and calcium, and a large amount of black residue.

Dog 8—A cannula with a bulb ( $\frac{1}{3}$  inch by 2 inches [0.8 by 5 cm]) was inserted. The observation covered ten days. The dog had distemper. It was killed.

*Postmortem Study*—The cannula was filled with dark bile of high viscosity and some evenly distributed coagulated matter. There was a dark, precipitated mass in the end of the bulb. Chemical examination of the precipitate showed some pigment, calcium, 1.5 per cent, and a large amount of black residue, unaccounted for. Analysis of bile from the gallbladder revealed a value for pigment of 125 mg and a value for calcium of 54 mg per hundred cubic centimeters. Bile from the bulb contained 78 mg of pigment and 37 mg of calcium per hundred cubic centimeters.

Dog 9—A cannula with a bulb ( $\frac{1}{3}$  inch by 2 inches [0.8 by 5 cm]) was inserted. The observation covered five and one half months. The dog was in good condition. It was killed.

*Postmortem Study*—There was some dilatation of the gallbladder. The common duct and the bulb were imbedded in omentum. A thick fibrous capsule covered the glass. When the common duct was opened the cannula was surrounded by thickened bile. The ligatures around the common duct had cut through the duct and were found on the cannula. The gallbladder contained dark bile and numerous black, friable concretions, measuring 1 to 3 mm (fig. 5). The cannula and the



Fig. 4 (dog 9)—Photograph, cannula with a bulb in the common duct at five and one half months. There was slight dilatation of the gallbladder and ducts. A, gallbladder, B, bulb arising from the cannula in the common duct, C, duodenum. Roentgenogram, same specimen. A, gallbladder, B, cannula, C, duodenum.

bulb contained liquid bile (with increased viscosity) and some coagulated matter. Chemical analysis of the concretions in the gallbladder showed a trace of cholesterol, a trace of pigment, calcium, 5.9 per cent, and a large amount of black residue, unaccounted for. Analysis of the coagulated matter in the cannula and in the bulb showed cholesterol, 5.3 per cent, pigment, 0.3 per cent, calcium, 0.3 per cent, a trace of phosphorus, and residue (by difference) 94 per cent.

Dog 10—A cannula with a bulb ( $\frac{1}{3}$  inch by 3 inches [0.8 by 5 cm]) was inserted. The observation covered five months. The dog was in good condition. It was killed.

*Postmortem Study*—The gallbladder and ducts were not dilated. A fibrous capsule had formed around the bulb. There was dark green bile with coagulated matter in the gallbladder.

#### COMMENT

Though the flow of bile in the glass bulbs was slowed, the changes in the bile were slight and inconsistent. The bile remained liquid in all bulbs, and in only 2 instances (dogs 8 and 9) was its viscosity markedly increased. Precipitation had occurred in only 2 instances, once in the form of a dark sediment (dog 6) and once as a precipitated mass

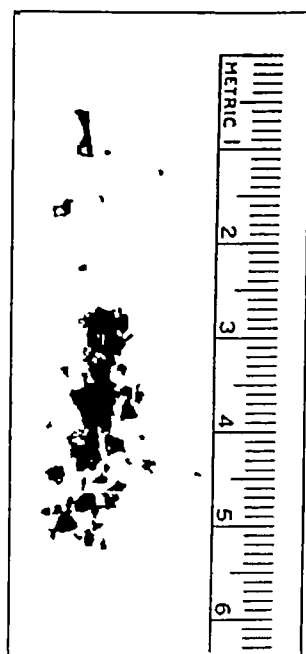


Fig 5 (dog 9)—Concretions found in the gallbladder, resulting from partial obstruction of the common duct. The cannula had been inserted in the common duct for five and one-half months.

(dog 8) weighing 8 mg total. This mass was low in calcium but contained a large amount of residue. In dog 7 a small concretion of similar composition was found on the edge where the cannula and the bulb connect. Both of these resembled the incrustations on the cannula described in the first part of this study.

Concretions in the gallbladder itself were found in 1 experiment, in which the cannula had caused partial obstruction of the duct with marked dilatation of the gallbladder. These concretions contained comparatively much calcium (5.9 per cent) and resembled the concretions formed in the gallbladder of the dog in which stenosis of the common duct had been produced by a cannula.

## SUMMARY

In 3 dogs with a glass cannula inserted in the common duct after cholecystectomy the flow of bile remained fairly normal during an observation period of from sixteen months to two years

The cannula had worked out of the duct in 2 other cases in which the gallbladder had not been removed

One animal of group 2, showing slight stenosis due to scar formation in the common duct and dilatation of the gallbladder, revealed two small concretions in the gallbladder. These concretions contained a fair amount of calcium and cholesterol, some pigment and a large amount of unidentified black substance.

When cholecystectomy was combined with implantation of the cannula, the cannula remained in place in the duct, and incrustations formed on its inner and outer surfaces, but only a small amount of obstruction occurred. The incrustations contained little calcium, a trace of cholesterol and bile pigment and a large amount of unidentified black residue. Local bile stasis and the presence of a foreign body seem to have played a part in their formation.

When bile stasis is produced by inserting a glass cannula into the common duct with a large diverticulum-like attachment, the bile in this "diverticulum" usually remains liquid, and only occasionally are small precipitations found.

## CONCLUSION

While it cannot be stated that true gallstones were produced by these experiments, deposits were obtained in the gallbladders and common ducts of dogs which bore some resemblance to calculi.

# CAUSE OF DEATH IN CASES OF MECHANICAL INTESTINAL OBSTRUCTION

CONSIDERATION OF CERTAIN CONFUSED ISSUES AND  
REVIEW OF RECENT LITERATURE

EDWARD L. BESSER, M.D.

IOWA CITY

One who studies the literature on the cause of death in cases of intestinal obstruction finds confusion and conflicting opinions concerning many phases of the problem. This fact was the stimulus for writing this paper, the purpose of which is to consider the experimental studies that have been made since Cooper's review of the subject in 1928 and to present the present status of knowledge concerning the problem. In order to discuss many of the confusing issues, some of the older work will be considered.

In most instances of clinical obstruction and in the various types of experimental obstruction, death occurs before gross perforation of the intestine has taken place, and under these circumstances the cause of death cannot be satisfactorily explained by the autopsy observations. The course has been described as that of "toxemia," and for many years it was generally accepted that the cause of death from all types of obstruction was the absorption of some toxic substance from the gastrointestinal tract. However, recent studies have suggested that different types of obstruction may cause death by different mechanisms.

## SIMPLE HIGH INTESTINAL OBSTRUCTION

After a duodenal or a high jejunal obstruction has been made, there is a symptomless period of eighteen to twenty-four hours or longer, and then the picture of the so-called "toxemia of high obstruction" develops. The obstruction prevents the absorption of food and the secretions of the upper part of the intestine, and vomiting is marked. The animals become greatly dehydrated and show tremors and weakness of the hindlegs, the pulse becomes weak and rapid, the blood pressure falls, the urine is scanty, and coma usually precedes death (Cooper). The average period of survival is five days. Obstruction of the duodenum just below the opening of the pancreatic and common bile ducts causes the most acute onset of symptoms and the earliest death.

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This paper was written during the tenure of a fellowship in surgery at the Johns Hopkins University and an assistant residency in surgery at the University Hospitals, Iowa City. Dr. Ferdinand C. Lee has made many helpful suggestions.

The periods of survival with lower obstructions are in a general way proportional to their proximity to this point. This was established by Draper, and the point under discussion is often called the "lethal line of Draper." It has been amply confirmed (Dragstedt, Lang and Millet, Dragstedt, Moorhead and Burcky). At autopsy there is "congestion" of all the viscera, but congestion of the duodenal mucosa is particularly prominent. However, there are no pathologic observations that are sufficient in themselves to be the cause of death. Definite alterations in the composition of the blood have been reported by many investigators, and some of these are fairly constant. A fall in the concentration of chlorides, an increase in nonprotein nitrogen and evidence of hemoconcentration are found in all cases of high obstruction (Gamble and Ross, Haden and Orr). There is always some degree of alkalosis with pyloric obstruction, and this is variable if the obstruction is below the pancreatic ducts (McIver).

Death in cases of experimental high obstruction is essentially due to loss of water and sodium chloride and the resultant dehydration.

There is not universal acceptance of this postulate, but it is supported by most recent investigators, largely on the basis of three types of experiments.

1. The lives of dogs with high intestinal obstruction can be prolonged for over three weeks by parenteral injection of sufficient amounts of water and sodium chloride. This was first shown in 1912 by Hartwell and Hognet and was substantiated by Haden and Orr, who found that under these conditions the blood chemistry remained essentially normal. The loss of fluid cannot be made up by administration of water alone or of solutions of dextrose, sodium bicarbonate, ammonium chloride, calcium chloride or other ions (Foster, Gamble and Ross, Gatch, Trusler and Ayers, Haden and Orr). Physiologic solution of sodium chloride is in general most satisfactory, and concentrated solutions of sodium chloride prevent a marked fall in the blood chlorides but do not significantly prolong survival (Gatch, Trusler and Ayers, Schnohr).

*Mechanism of Dehydration* — This was carefully studied by Gamble and Ross, McIver and Gamble, and Atchley and Benedict, and this work was summarized by McIver in 1934. It was noted that losses of sodium and chloride ions were in themselves largely responsible for the dehydration and alkalosis. The volume of a body fluid is sustained by its total ionic content. Quantitatively the chief factors making up the total ionic content of the digestive secretions, blood plasma and intercellular fluids are the sodium and chloride ions. Under the conditions of obstruction a marked depletion of sodium and chloride occurs, and thus a depletion of the total ionic content of the plasma and of the intercellular fluids takes place. This is of necessity accompanied by a

parallel loss of water. In other words, dehydration is regarded as a result of loss of the electrolytes sodium and chloride. In order to restore and sustain the original volume of blood plasma and the intercellular body fluids, there must be replacement of the lost electrolytes. Gamble and Ross substantiated their theory by experiments in which they showed that a large amount of sodium as well as of chloride is lost in the vomitus and that there is definitely a lowering of the sodium content of the serum. In the production of dehydration, loss of the sodium ion is much more significant than loss of the chloride ion. The decrease in the total ionic content caused by loss of the chloride ion is quickly compensated by an increase of bicarbonate ion. There is no comparable mechanism for replacement of the sodium ion.

The alterations in acid-base equilibrium are governed by the proportion in which the sodium and chloride ions are lost. The sum of the acid ions in the plasma must be equivalent to the total of basic ions. Sodium accounts for over 90 per cent of the basic ions. If the quantity of the ions is changed, this equivalence is maintained by the adjustability of the bicarbonate ion. In the presence of pyloric obstruction the chloride ion is lost to a greater extent than is the sodium ion (owing to loss of hydrochloric acid in the vomitus), and the excess of the basic ions (mostly sodium) is covered by an increase in the bicarbonate ion, thus there is alkalosis. In the pancreatic juice and in the bile there is a larger amount of fixed base (sodium) than in the gastric juice, and this increased sodium is balanced by the bicarbonate ion. Therefore, loss of these secretions tends to reduce plasma bicarbonate and to cause acidosis. Thus in the presence of high duodenal or jejunal obstruction the presence or absence of alkalosis or acidosis will vary with the relative loss of gastric juice on the one hand and of bile and pancreatic juice on the other. In the presence of high obstructions the loss of gastric juice is usually greater, and hence alkalosis usually occurs.

The lowering of the level of blood sodium and chloride is adequately explained by the amounts of sodium and chloride recovered in the vomitus (Gamble and Ross, Gatch, Trusler and Ayers, Raine and Perry). The marked electrolyte loss occurs during the early, or "critical," period of obstruction, since it was shown by Foster and Hausler that when dogs with simple high obstruction are given sufficient amounts of physiologic solution of sodium chloride for only the first four or five days they will survive three or four weeks and show no hypochloremia. This has been confirmed by others (Gatch, Trusler and Ayers, Wangenstein and Chunn). There is no definite "lethal level" of blood chloride or sodium. The values found in blood specimens taken just before death vary markedly. McIver stressed the fact that the level of the blood chlorides is not a true measure of the total extent of dehydration of the body. The loss of plasma electrolytes is replaced



from the intercellular fluids, and it has been found that a marked reduction in water content of the subcutaneous tissues and of the skin occurs in cases of high obstruction (Miller) These tissues are abundant sources of intercellular fluids

2 The survival of animals with high intestinal obstruction has been markedly prolonged by administration of vomitus and dextrose or other solutions containing sodium chloride and food into an enterostomy below the obstruction or by shunting the secretions of the upper part of the intestine below the obstruction Jenkins and his co-workers have done a number of such experiments With 2 dogs, survival periods of fifty-two and seventy days respectively were attained by jejunostomy feedings below the obstruction Similar experiments have been done by several other groups of investigators (Armour and others, Pearse, White and Fender)

3 Animals with high intestinal fistulas die in the same length of time and show the same symptoms and almost the same changes in chemical composition of the blood as do animals with high intestinal obstruction and their lives may be markedly prolonged by the administration of physiologic solution of sodium chloride This has been demonstrated by Walters, Kilgore and Bollman and substantiated by others (Dragstedt and Ellis, Morton and Pearse) Morton and Pearse contended that "it is necessary to assume that either there is a toxemia present in both high intestinal obstruction and fistula at the same level, or that there is no toxemia in either"

*Objections to the Theory that Death from High Intestinal Obstruction Is Due to Electrolyte Loss and Dehydration* — Investigators have attempted to produce in normal dogs electrolyte loss and dehydration comparable to those found in cases of high intestinal obstruction by gastric lavage and by inducing vomiting with such drugs as pilocarpine Earlier workers found that dogs could be apparently dehydrated, yet show little evidence of intoxication and quickly recover when given food and water (Ingvaldsen and others) No blood studies or attempts to determine quantitatively the degree of dehydration were made, but recently Taylor and others, using similar methods, obtained blood chloride levels as low as 260 mg per hundred cubic centimeters and maintained them for several weeks without obvious intoxication However, it has been noted that the level of blood chloride is not a true measure of dehydration, and hence these experiments can hardly refute the dehydration hypothesis

#### LOW INTESTINAL OBSTRUCTION

Experimental low ileal obstruction usually produces a picture quite different from that of high obstruction Although in some dogs vomiting and other symptoms come on rapidly and simulate high obstruction,

the majority of animals vomit little, remain in apparent good condition for seven, eight or nine days and then often die abruptly. The usual range of survival is from two to fourteen days, but there is wide variation (Eisberg and Diaper, Elman and Hartmann, Hartwell and others). Attention has been called to the fact that low ileal obstruction in dogs differs from low ileal obstruction in human beings in that the latter almost always brings on acute symptoms and vomiting, and if obstruction is complete the survival is not likely to exceed a few days (McIver). The autopsy observations do not adequately explain death. The most intensive study of the general picture and blood chemistry in the presence of low ileal obstruction is that of Elman and Hartmann. They found that occasionally some dogs vomited and showed a decrease in blood chlorides, hemoconcentration and evidence of dehydration, but these changes were absent in the majority. Parenteral injection of saline solution did not prolong survival. The last-mentioned finding was in confirmation of the earlier work of Hartwell and his associates. Holt, however, stated the belief that electrolyte loss and dehydration play a more significant role in low ileal obstruction than is generally believed and was able to obtain an average survival time of twelve days in a series of 11 dogs to which adequate amounts of physiologic solution of sodium chloride were given. Elman and Hartmann concluded that "death seems due to a profound peripheral circulatory failure or 'shock' which is quite distinct from the circulatory impairment due to dehydration in the case of high obstruction." Most investigators have expressed the belief that in the presence of low ileal obstruction the absorption of toxic material is the most significant lethal factor, but conclusive proof of this hypothesis has never been attained.

Under what conditions of the intestinal mucosa may a toxic substance be absorbed? The normal intestinal mucosa is impervious to any of the various toxic substances obtained from obstructed intestinal contents (Cooper). Many investigators have contended that toxic absorption does not take place until there are definite microscopic changes in the intestinal mucosa. However, others have stated that the selective absorption of the mucosa may be altered before visible evidence of pathologic alteration has taken place. One approach to this question is to study the histologic changes that take place in the mucosa under the conditions of obstruction. Many of the studies cited in the literature were made when it was generally believed that death from all types of obstruction was due to absorption of toxins and when there was little appreciation of the possibility that electrolyte loss and dehydration per se might cause death in certain instances. The majority of investigators of the earlier group reported marked mucosal changes, with intarction and ulceration in cases of experimental obstruction (Cooper, Van Beuren). However, in most instances no note was made

of the various levels of obstruction. Recently Carlson and Wangensteen studied the histologic structure of the bowel wall from autopsies on 35 dogs with simple obstruction at various levels. They found no evidence that "loss of epithelium is a marked or constant characteristic of simple obstruction and necrosis of the bowel wall did not occur in any of the series." Elman and Hartmann, in their study of ileal obstruction in dogs, reported that death occurred without "demonstrable lesions of the obstructed wall or mucous membrane" in over half of the dogs of their series. Thus recent investigation suggests that death in cases of simple intestinal obstruction may occur without definite microscopic mucosal changes. In cases of high obstruction, in which it is generally believed that death is due to electrolyte loss and dehydration and distention is relieved by vomiting, one might expect that death might well occur before mucosal changes took place. One is tempted to postulate that electrolyte loss and dehydration played a part in causing death in the dogs with low ileal obstruction that did not show mucosal changes. This possibility, although not discussed in the reports of Wangensteen and Carlson and of Elman and Hartmann, undoubtedly occurred to these authors. Holt gave dogs with low ileal obstruction large amounts of physiologic solution of sodium chloride and observed mucosal changes in all the dogs at autopsy. The relation between the intoxication associated with intestinal obstruction and the mucosal changes is not definitely established.

*Role of Distention in Low Ileal Obstruction*—Several groups of investigators have measured the intraintestinal pressure during obstructions (Morton, Owings and others, Sperling). In general it has been found that pressures between 4 and 19 cm. of water are found in dogs with low ileal obstruction, and Sperling found similar sustained pressures in clinical cases. In these cases peristalsis caused the pressure to rise to 30 cm. of water. Obstruction of the large bowel caused higher pressures, owing to the fact that the ileocecal sphincter made the colon virtually a closed loop. As obstruction proceeds, fluids and gases collect in the lumen. Whether distention augments or inhibits intestinal secretion is a controversial point (Gatch and Culbertson, Herrin and Meek, Montgomery and Swindt). The intestinal gases are derived from swallowed air and from digestive processes. An active diffusion of gases between the blood and intestinal lumen takes place according to the laws governing gases. Diffusion of oxygen and carbon dioxide from the lumen into the blood takes place, and these gases are replaced by nitrogen, which comes from the blood stream (McIver and others). Practical application of this fact is found in the experiments of Rosenfeld and Fine, who found that the nitrogen in the intestinal lumen could be displaced by breathing pure

oxygen. An increase of the survival period in animal experiments was reported, and encouraging results were obtained in using this method for the clinical treatment of postoperative distention (Fine and others). Hibbard, working in Wangenstein's clinic, made a number of studies of the intestinal gases in the presence of obstruction. He discovered that under the conditions of obstruction gases of the volatile basic group (ammonia, methylamine and tertiary amines) were found. In an earlier report, Hibbard concluded that the volatile basic group of gases were harmless in the concentrations present in obstruction. Later, Hibbard and Kremen reported that a distillate containing the volatile bases and buffered at a specific  $p_H$  caused death when injected into closed loops of intestine of a normal dog. However, absorption seems dependent on an optimum  $p_H$ , which has not been shown to occur in the presence of an obstructed intestine. Few studies have been made in this respect, hence the role of the volatile gases as a toxic factor cannot be settled at this time.

*Effects of Measured Intraintestinal Pressure on Microscopic Appearance and Permeability of the Bowel Wall*—Many ingenious methods of distending the intestine and observing the effects have been carried out. In general, for each increase in intraintestinal pressure there is a corresponding decrease in the volume of blood per minute circulating through the wall (Dragstedt and others, Gatch and Culbertson, Gatch, Owen and Trusler). Sperling distended loops to pressures known to exist in cases of experimental and clinical obstruction (20 cm for twenty-four hours) and found that necrosis, loss of viability and abnormal permeability of the wall occurred. He noted that viability (as tested by response to faradic current) was lost before the wall became directly permeable to potassium ferrocyanide.

*Effect of Distention on Blood and Plasma Volume*—Aird made studies of the blood and plasma volumes in cases of low ileal obstruction and found significant decreases but did not conclude that these were of such proportions that they could be the lethal factor per se. Recently, however, Gender and Fine have reported that average losses of plasma volume of 55 per cent occurred in cases of experimental low ileal obstruction and have postulated that death can be attributed to this decrease of plasma volume per se.

#### ABSORPTION IN CASES OF INTESTINAL OBSTRUCTION

The possible avenues of absorption of a toxic material are (1) direct permeation of the wall, usually referred to as "transperitoneal absorption", (2) absorption through the mesenteric vessels, and (3) absorption through the lymphatics. Absorption in the presence of obstruction has been studied largely by introducing various substances

into the lumen and subsequently testing for their absorption or attempting to demonstrate toxic factors in the body fluids. Many substances have been used, and many methods of testing for their absorption have been devised. Certain generalizations may be made.

1 Transperitoneal absorption of toxic material occurs only through nonviable bowel.

This general statement has been made by a number of investigators (Gatch and Culbertson, Gatch, Owen and Trusler, Sperling and Wangenstein, Wangenstein). These investigators found that certain dyes and potassium ferrocyanide did not pass through the wall until it was nonviable. However, difficulty arises in defining the term "viable." The fact that viability is present as indicated by muscle contractions possibly may not mean that every other physiologic characteristic of the intestine, such as mucosal selectivity, is functioning normally (Jacques and others).

2 There are no experimental results which suggest that absorption of any substance normally absorbed is increased in the presence of obstruction.

On the contrary, there are many reports that the absorption of such substances as calcium iodine, (Clairmont and Ranzi), strychnine (Wangenstein), sodium chloride (Enderlen and Hotz) and phenol-sulfon-thalein (Palma) is decreased in the presence of obstruction.

3 Is there any experimental proof that under the conditions of intestinal obstruction substances are absorbed that are not absorbed by normal intestine?

Tests have been made for the absorption of such substances as histamine, epinephrine, acetylcholine and colloidal graphite. In general, there is no evidence that obstruction allows absorption of these substances (Carlson and others, Dobyns and Dragstedt, Wangenstein and Loucks). However, Haerem, Dack and Dragstedt have recently found that the toxin of *Clostridium botulinum* could be demonstrated in the blood after being injected into an obstructed loop. In comparable quantities this toxin was not absorbed from the normal dog intestine. They noted that gross necrosis of the distended segments did not always occur when the toxin was demonstrated in the blood stream. This suggested that abnormal absorption, in this instance at least, was not dependent on visible microscopic degenerative changes of the mucosa. In a comparable type of experiment, Hettwer and Hettwer sensitized guinea pigs to horse serum. After injection into an obstructed loop of such a dose as was noneffective when introduced into normal intestine, it was found that absorption occurred, as shown by the anaphylactic reaction which took place. Thus there is some experimental evidence that abnormal absorption occurs in the presence of obstruction, but its correlation with the state of the mucosa is not definite.

4 Lymphatic absorption is increased in cases of intestinal obstruction, and certain substances are absorbed through the lymphatics that are not absorbed by the normal intestine

Certain dyes and bacteria which are absorbed by the normal intestine have been found in the lymph nodes in various cases of experimental obstruction (Sperling and Wangersteen, Stone and Firor) It is an accepted physiologic principle that increased intraluminal pressure and associated increased mesenteric venous pressure cause increased lymphatic absorption Some investigators have explained this absorption largely on the basis of stasis and have stated that in normal intestine absorption is prevented by the rapid transit of the material through the bowel In 1915 Murphy and Brooks recovered toxic material from the thoracic ducts after having injected such material into a loop which was subsequently distended There are no reports that this interesting experiment has been repeated

*Recovery of Toxic Materials in Body Fluids*—If there is absorption of toxic material in cases of simple obstruction, it would seem plausible that in some manner such material could be recovered from the body fluids A few such positive claims have been made, but it may be stated that as yet no one has conclusively shown the presence of toxic material in the body fluids in cases of simple obstruction The entire blood content of toxic animals with various types of obstruction has been transfused into normal animals without effect (Carlson, Lynch and Wangersteen, Foster and Hausler, South and Hardt) A few positive claims have been made concerning the recovery of toxic material from the peritoneal fluid and the lymph (Schonbauer), but these were not confirmed by other workers (Dragstedt and others, Murphy and Brooks, Murphy and Vincent, Traum) Sugito and Scholefield reported the presence of a toxic substance in the mesenteric veins of a closed loop in the terminal stages of obstruction, but their experiments have been criticized from several points of view and have not been further confirmed

#### ISOLATED CLOSED LOOPS

If a segment of small intestine is isolated, the ends inverted and the continuity of the intestinal tract is reestablished by anastomosis, the animal will present a picture in a general way similar to that of an obstruction at the level from which the segment was isolated

This statement was expressed by Cooper and is well substantiated (Bunting and Jones, Dragstedt and others, Murphy and Brooks, Stone and others) However, there are certain variations Dogs with duodenal loops present a rather consistent clinical picture, the period of survival is fairly constant (between forty-eight and ninety-six hours), and death usually occurs before the loop perforates At autopsy

splanchnic congestion is prominent, but few observers have reported more marked changes than congestion in the various organs. Short jejunal loops present a picture similar to that of duodenal loops but perforation more frequently occurs before death ensues. Survival is in a general way directly proportional to the length of the loop, and long jejunal loops are associated with wide variations in survival (Thurston). When long loops are made, death frequently occurs before perforation takes place. Low ileal and colonic loops are often tolerated for weeks with relatively few symptoms (Copee, Gatch and others, Murphy and Brooks, Whipple, Wilkie). When short loops are made high in the intestine, there are rapid distention and marked anorexia and vomiting. Changes in the blood chemistry are found which are similar to those reported in cases of simple high obstruction (Dragstedt, Haden and Orr). Burget noted that relief of the distention by aspiration relieved the anorexia and vomiting. Dehydration may be a factor in causing death under these circumstances, but definite mucosal changes are observed at autopsy, and life cannot be prolonged by parenteral fluids, because if these are given the loops will soon perforate. When long jejunal loops (over 35 cm.) are made, the animals become weak, lose their appetite, lose weight, become asthenic and often die of distemper (Thurston). The loops are usually greatly distended, but reports vary as to the state of the mucosa. However, most investigators feel that death is due to slow absorption of toxic material.

#### NATURE AND ORIGIN OF TOXIC SUBSTANCE IN THE INTESTINAL LUMEN

The contents above an obstruction, from isolated closed loops or from strangulated loops, are toxic when injected into a normal animal.

There is little in the literature to suggest that this statement would not be universally accepted. The word "toxic" is often loosely used in the literature and may mean anything from a transient depression of the blood pressure to actual death. The course, symptoms and eventual outcome have varied widely in the hands of different investigators. Crude material obtained from the lumen of the obstructed intestine is almost always toxic and is usually lethal when injected intravenously, when it is injected intraperitoneally it usually causes the same picture, but the effect is more prolonged and peritonitis is a conflicting factor (Habler, Knight). There are many obvious objections to conclusions drawn from this sort of experiment, and most investigators have attempted to obtain a more purified material. Thus filtrates, supernatant fluid from centrifuged specimens and detailed chemical methods have been used to obtain purified products. In general, these have led to more consistent results in the hands of those who have used them, but variations were found in that various investigators isolated materials

that had different chemical and pharmacologic actions. However, the majority of investigators have found that their toxic material was water soluble, heat stable, largely removed by a Berkefeld filter and precipitated by alcohol. The following substances have been reported to have been recovered from toxic obstructed material: choline and neurine (Nesbitt), a heteroproteose (Whipple), a nucleoprotein (Ingvaldsen and his co-workers) and histamine (Gerard). The preponderance of opinion is that the toxic substances which most investigators have found in obstructed contents are either secondary, derived products of protein decomposition (the proteoses) or amines which are formed by bacterial action. Whipple and his various co-workers contended that the toxic material is a heteroproteose and later that it is nucleoprotein but that it is definitely not histamine. On the other hand, Gerard contended that the properties of the obstructed content can be accounted for by their content of free and combined histamine, although he expressed the opinion that other toxins are also present. Gerard recovered significant amounts of histamine from closed intestinal loops. These variations suggest that there may be several toxic substances existing under different conditions.

The crude substance of the various toxic preparations may be introduced into the lumen of the normal small intestine with no untoward results. This postulate was expressed by Cooper and is generally accepted.

The question then obviously presents itself: Are normal intestinal contents toxic when injected intravenously or intraperitoneally? In Cooper's review the general statement was made that they are not toxic or are only slightly so. In reviewing the original papers, the author found that many of the investigators generally referred to as supporting this contention had limited their work and in most instances their conclusions to the secretions of the intestinal mucosa per se (Davis and Stone, Dragstedt and others) or to the toxicity of autolyzed normal mucosa. Much of the early work has been repeated, and the more recent experiments show that both normal and obstructed contents are toxic (Van Beuren, Gatch, Trusler and Lyons, Wangenstein and Chunn), their toxicity depending on the method of preparation of the material and the manner of injection. Gatch and his co-workers have reported that the contents of the higher part of the small intestine are highly toxic and those of the lower part much less so. They have found that the normal combined pancreaticoduodenal secretion is highly toxic and usually lethal when injected into a normal animal. The experiments of other investigators have offered confirmatory evidence concerning the toxicity of the normal pancreaticoduodenal secretion or the activated pancreatic juice (Bottin, Cybulski and Tarchanoff, Sugito, Sweet).



*Toxicity of Obstructed Contents*—Although the pancreaticoduodenal secretion may be the primary factor in causing the toxicity of normal intestinal content, there is reason to doubt that it plays the sole role in causing the toxicity of the contents above a low ileal obstruction. These contents are toxic in obstructed dogs from which the pancreas has been previously removed (Ingvaldsen and others). The secretion of the duodenum per se has not been found toxic (Davis and Stone), and there is little to suggest that the other intestinal secretions are very toxic.

*Role of Ingested Food*—Hibbard and Kremen have reported that survival of obstructed dogs is decreased if the animals are fed high protein diets. Certain early reports stated that the intestinal contents are highly toxic after diets high in meat and only slightly toxic after diets of only milk (Dobyns and Dragstedt). However, Habler has recently reported that protein-free nourishment did not alter the period of survival. Thus the relation of ingested food to the toxicity of obstructed intestinal contents is obscure, but certain of the intermediary products of digestion are toxic, and there are no experiments which prove that these substances do not make some contribution to the toxicity of obstructed contents, although the general consensus is that their toxicity is of secondary importance.

*Bacterial Origin of the Toxin*—Cooper stated in his review in 1928 that "the preponderance of opinion seems to be that bacteria play an essential role in the formation of the toxic substances in obstructed intestinal content." The basic experiments which substantiated this contention were those of Dragstedt and his co-workers, who were able to autosterilize isolated loops by leaving them open in the abdominal cavity. These loops could then be closed or even strangulated without causing symptoms.

*Toxicity of Autolyzed Intestine*—If, in any type of obstruction, the circumstances are such that the wall has become nonviable, the subsequent process of autolysis is intensely toxic. Bacteria have been shown to play an essential role in this process. If segments of bowel are excised, washed with the usual antiseptics and returned to the peritoneal cavity, death quickly ensues (Wangensteen and Waldron). It is almost impossible to sterilize segments of intestine by this means (Dragstedt, Moorhead and Burcky, Dragstedt, Dragstedt, McClintock and Chase, Scott). However, Scott sterilized segments in the autoclave, and such segments caused no ill effects when placed in the abdominal cavity. It seems that these experiments offer valid evidence that the toxicity of autolyzing intestine is dependent on bacterial action.

*Role of Bacillus Welchii*—Williams in 1926 contended that the absorption of *B. welchii* toxin is an important factor in causing death

in cases of intestinal obstruction. Although he reported a mortality of 95 per cent in a series of cases treated with B welchii antitoxin, there has been no satisfactory confirmation of the clinical value of the antitoxin in cases of obstruction. Experimentally, the survival of obstructed animals has not been prolonged by the antitoxin (Holt, Owings and McIntosh), and investigators have failed to find immune bodies in the serum of animals with intestinal obstruction (Thurston). The preponderance of recent work shows that there is little evidence that the toxin of B welchii is the primary factor in intestinal obstruction.

*Summary*—The toxicity of normal intestinal contents is largely due to the toxicity of combined pancreaticoduodenal secretions and possibly to some of the intermediary products of digestion. The toxicity of obstructed contents which receive and retain the pancreaticoduodenal secretions may be due primarily to the presence of these combined secretions. However, the toxicity of obstructed contents in cases of low intestinal obstruction is more likely due to histamine, histamine-like substances from bacterial putrefaction or secondary, derived products of protein decomposition. If an obstruction has proceeded to such an extent that the wall is nonviable, the subsequent autolysis is highly toxic. This toxicity is apparently dependent on bacterial action.

#### STRANGULATION

Death frequently occurs in cases of experimental strangulation before gross perforation occurs. The period of survival is governed by the length of the loop and the type of strangulation. In general, the longer the loop, the shorter the survival (Aird, Foster and Hausler, Wahren). The type of strangulation is more significant than the length of the loop. Thus the following average periods of survival were noted by Scott and Wangenstein for the various types of strangulation that have been studied.

	Length	Hours
Group 1. Encirclement with a rubber band about the mesentery	1 to 5 feet (30 cm. to 1.5 meters)	4
Group 2. Ligation of arteries and veins	1 to 5 feet (30 cm. to 1.5 meters)	20
Group 3. Ligation of arteries alone	1 to 4 feet (30 cm. to 1.2 meters)	20
Group 4. Ligation of veins alone	3 to 5½ feet (91 cm. to 1.6 meters)	5

*Composition of Blood*—Death occurs in the absence of dehydration, and there are no marked alterations in the blood chemistry other than a moderate increase in nonprotein nitrogen (Cooke and others, Hatch, Tusler and Ayers).

*Significance of Loss of Fluid*—Holt measured the amount of fluid lost in strangulated loops by enclosing them in a rubber bag and con-

cluded that in the long loops enough fluid was lost to cause death per se. Knight and Slome opposed this postulate by stating that if a toxic factor caused death in the short loops it would also be a factor with the longer loops. They objected to Holt's experiments on the basis that the rubber bag prevented reabsorption of the peritoneal fluid. They measured the loss of fluid by weighing the loops and swabbing the peritoneal cavity with cotton swabs of known weight. It was concluded that, regardless of the length of the loop, "there was no constant relations between the amount of fluid lost from the circulation and the survival time." However, Scott used a method similar to that of Knight and Slome and found that in strangulations of two types, encirclement of the mesentery with rubber bands and ligation of the veins alone, the loss of blood itself was sufficient to cause death, but this was not true with the types in which the arteries or both the arteries and the veins were ligated. These studies were based on the postulate of Blalock that a loss of fluid equivalent to 4 per cent of the body weight must occur to cause death from fluid loss alone. Although there is dissension as to the relative role of fluid loss and strangulations, these experiments would lead one to feel that with long loops, at least, the loss of fluid is in itself sufficient to cause death.

*Recovery of Toxic Factors in Body Fluids*—If the strangulation is sufficient to shut off the lymphatics and the venous return, it would seem that if absorption of a toxin occurs it must be by means of transperitoneal absorption. Under these conditions one would expect that toxic materials would be present in the peritoneal fluid. However, this has been rather difficult to demonstrate. Scott and Wangenstein injected untreated peritoneal fluid from dogs that had died of strangulation without rupture into normal dogs (intravenously) and found no immediate or delayed effects. In experiments in which the loops had ruptured, there were innumerable bacteria, and the animals died of a generalized gas bacillus infection. On the other hand, Knight and Slome reported that fluid collected by means of a rubber bag placed about a nonviable loop caused a marked and sustained depressor effect on a normal cat's blood pressure and in large doses was lethal. Knight reported that samples of peritoneal fluid from cases of strangulation in human beings caused a "depressor" action when injected in small amounts into anesthetized cats. Some of the samples caused only a transient depressor effect but those from patients with gangrenous segments of intestine caused the blood pressure to remain at a "permanently low level."

Wahren found that fluid from a rubber bag about strangulations in rabbits when injected into a normal rabbit caused a state of shock which was sometimes lethal. Aird and his associates also found such fluid to be toxic.

The period of survival in cases of strangulation of small and medium-sized loops is increased by enclosing the loops in a rubber bag (Foster and Hausler, Holt, Wahren) The usual interpretation is that the rubber bag prevents absorption of toxic material

*Nature of the Toxic Material Collected in Such Rubber Bags*—Wahren reported that histamine, acetylcholine, adenylic acid and other known depressor substances are not present in significant quantities and that it is probable that a markedly toxic substance not yet chemically defined is responsible for the toxic properties of such fluids Aird reported isolation of two chemical compounds from such fluid that produced toxic effects when injected into normal animals One appeared to be a protein of the euglobulin class, while the other resembled histamine Later, Aird and Henderson reported that "the histamine content of the transudate from strangulated loops was exceedingly high but histamine could not be regarded as the sole lethal factor in intestinal strangulation"

Several investigators have called attention to the fact that it is difficult to evaluate the role of substances recovered from such fluid by injecting them into normal animals, because the strangulated animal will have more or less loss of blood volume and perhaps other such factors that would cause lessened resistance (Aird and Henderson, Maycock) Thus Maycock found that the acute depressor effects of such fluid could be accounted for by the amounts of histamine and choline present but that these quantities were not great enough in themselves to produce lasting harmful results He found that slow intravenous injection of such peritoneal transudates into the normal anesthetized animal whose volume of total circulating fluid has been diminished causes death, while intraperitoneal injection of such peritoneal transudate into unanesthetized animals whose volume of total circulating fluid has been diminished in most instances produced no harmful effect

*Recovery of Toxic Factors from Portal Venous System*—Knight and Slome have reported the recovery of substances which had a marked depressor action from the superior mesenteric vein when the entire small intestine of a cat was strangulated Knight has recently reported that blood taken from the mesenteric veins of segments of strangulated gangrenous human intestine caused a depressor effect The nature and significance of these depressor materials is open to question on the basis of the technical details of the experiment (Maycock)

ROLES OF A NEURAL MECHANISM AND SHOCK, PATHOLOGY AND  
PHYSIOLOGY OF THE SPECIAL ORGANS ROLE OF HYPERPOTASSEMIA

Burget and Herrin and Meek have presented evidence which suggests that reflexes initiated by distention may play a significant role in

causing the anorexia and vomiting associated with obstruction Laylor and his associates produced "distention without obstruction" by means of a balloon fastened about a rubber tube When the distended portion of the intestine was denervated, survival was prolonged These authors suggested that a neural reflex played a definite role but did not discuss the mechanism Criticism of these experiments has been made by noting that the pressure to which the balloon was distended (100 mg of mercury) would certainly cause changes in the bowel wall (Knight and Slome)

*Role of Shock in Intestinal Obstruction*—Moon and Morgan have written the most extensive paper on the role of shock in obstruction They concluded that "intestinal obstruction is one of the many conditions which will produce characteristically the shock syndrome" They reported that study of autopsy material in cases of clinical and experimental obstruction revealed the capillary engorgement that is spoken of as characteristic of shock They reported an increase in capillary permeability to trypan blue in the terminal phases of intestinal obstruction These authors did not suggest that the role of shock might differ with the various types of obstruction and that there is reason to believe that the terminal prostration in cases of different types of obstruction may be caused by different mechanisms Thus Elman and Hartmann stated that in cases of low ileal obstruction "death seems due to a profound peripheral circulatory failure or shock, which is quite distinct from the circulatory impairment due to dehydration in the case of high obstruction"

*Elevation of the Nonprotein Nitrogen Content of the Blood and Pathology and Physiology of the Kidneys in Intestinal Obstruction*—An increase in the nonprotein nitrogen content of the blood is associated with all types of obstruction The values are variable and are not such that they can be considered the cause of death per se The elevated concentration of nonprotein nitrogen is thought by most recent authors to be secondary to the dehydration which accompanies simple obstruction or to the breakdown of body tissue associated with strangulation Certain workers have postulated impairment of the kidneys as a result of the action of an absorbed toxin (Brown and others, Fox and his co-workers, McQuarrie and Whipple), and some have found pathologic alteration in the kidneys (Brown and others) and impairment in renal function tests (McQuarrie and Whipple), but the prevalent opinion is that these changes are more likely due to dehydration than to the action of a toxin This, however, is still a controversial point

*Role of the Liver in Obstruction*—Elman and Cole reported that there was central necrosis in a mild form in nearly all, and to a marked degree in 54 per cent, of a series of dogs with simple loop obstructions

Similar but more consistent changes were found in cases of strangulation. Hepatic function tests showed slightly decreased values in the toxic stages of obstruction, but the earlier work of Werelius, which supported the contention that death in cases of obstruction is due to insufficiency of the liver, has not been confirmed by others.

*Role of Adrenal Glands in Obstruction*—Several workers (Scudder, Zwemer and Whipple, Wohl and others, Zwemer) have been impressed by the consistent cellular changes and lipid depletion observed in the adrenal cortex after death from experimental and clinical obstruction. Wohl and others found that dogs with high intestinal obstruction which were given adrenal cortical extract lived longer than did control dogs. It is well known that the adrenal cortex is essential for life and that it performs certain functions in the control of electrolyte balance and perhaps of capillary permeability. It is an attractive hypothesis that part of the terminal collapse in cases of obstruction may be due to adrenal cortical insufficiency, but as yet this is only a speculation.

*Role of Potassium in Intestinal Obstruction*—Scudder, Zwemer and Truskowski reported that in cases of both simple obstruction and strangulation they had found an elevation of the blood potassium to levels previously shown to be toxic. This led them to conclude that potassium is the toxic factor sought in cases of intestinal obstruction. Scudder and Zwemer found marked hyperpotassemia associated with intestinal fistulas and suggested that hyperpotassemia answers the hypothesis previously cited that there must be a toxin present with both high obstruction and high fistulas or absent with both. There is opposition to these views in the work of Bisgard and his associates, who found that the potassium levels became elevated in about half of their obstructed animals but noted that if potassium is the toxic factor it should be elevated in all instances of obstruction with toxemia. Two strangulation experiments were done, and in neither was an increase in potassium observed.

#### GENERAL SUMMARY

Attention is called to the fact that different physiologic and pathologic alterations take place under the conditions of different types of intestinal obstruction. The preponderance of evidence suggests that death in cases of high obstruction is due to the loss to the body of the secretions of the upper part of the intestine, the essential constituents being water and sodium chloride. Support for this contention is found in the fact that life can be markedly prolonged by replacement of these substances and only these substances. Experiments in which the intestinal secretions were short circuited around the obstruction substantiate this postulate, as does the fact that high intestinal fistulas cause a similar picture and respond in a similar manner.

In the presence of low intestinal obstruction there is opportunity for reabsorption, and, although dehydration and electrolytic loss may explain death in some instances, these factors do not seem adequate to explain death in the majority of instances. The general consensus is that death occurs as the result of absorption of toxic materials. Many investigators have contended that toxic absorption does not take place until there are definite microscopic changes in the intestinal mucosa. However, others have felt that selective absorption of the mucosa may be altered before visible evidence of pathologic alteration takes place. Recent studies have been reported, indicating that death in cases of low ileal obstruction occurs in the absence of marked changes in the intestinal mucosa. It has been suggested that electrolyte loss and dehydration may have been factors in the instances in which mucosal changes were not evident, although this has not been definitely established. The majority of experiments support the contention that there is no transperitoneal absorption or "direct permeation" of the intestinal wall as long as it is viable. Increased intraintestinal pressure tends to decrease absorption of substances normally absorbed by the intestine and has not been shown to cause absorption of most substances that are not normally absorbed. However, a few recent experiments have shown that increased intraintestinal pressures were associated with abnormal absorption of Cl botulinum toxin in dogs and of horse serum in guinea pigs. Lymphatic absorption is increased in the presence of obstruction, and certain dyes that are not normally absorbed are absorbed by the lymphatics under the conditions of obstruction. There is no conclusive proof that absorption of a lethally toxic material occurs by this route. In general there is no satisfactorily substantiated evidence of toxic materials in the body fluids in cases of low ileal obstruction. Animals with low ileal obstruction die in a state of "shock." There is a decrease in blood and plasma volume which is certainly of some consequence, but the precise role that these factors play is not definitely known.

Recent experiments have shown that normal intestinal contents may be as toxic as obstructed contents, or more toxic. The normal combined pancreaticoduodenal secretion per se is highly toxic. Although the nature and origin of the toxic material in obstructed contents is not clear, reasons are given for the belief that the pancreaticoduodenal secretions play a secondary role in respect to the toxicity of the material collected above a low obstruction. The preponderance of evidence suggests that the toxicity of this material is dependent on bacterial activity, and, although multiple toxins may be involved, part of the toxicity seems to be caused by the presence of histamine or a closely allied substance.

In strangulations of long loops the preponderance of evidence shows that the fluid loss per se may be great enough to cause death. How-

ever, with short loops and with death occurring before perforation, the fatal issue is probably due to absorption of a toxic material which is formed by the action of bacteria on the nonviable tissues of the intestinal wall. Although some experiments have been cited in which the peritoneal fluid was reported not to be toxic, a number of investigators have found toxic material in the peritoneal transudates. The nature of these transudates and their degree of toxicity have been variable. Histamine and comparable substances have been found in these transudates and cause depressor effects on blood pressure. No one substance has been proved sufficient in itself to cause death.

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# ACUTE METASTATIC SPINAL EPIDURAL ABSCESS

## REPORT OF TWO CASES WITH RECOVERY FOLLOWING LAMINECTOMY

DAVID L. REEVES, M.D.

LOS ANGELES

As can be appreciated from a review of the literature, the diagnosis, treatment and prognosis of acute metastatic spinal epidural abscess may be divided into two epochs. According to Van Den Berg,<sup>1</sup> the first of these, from the initial report of Morgagni<sup>2</sup> until the end of 1928, was, to say the least, despairing, for of 36 patients whose cases were reported only 1 recovered, a mortality of over 97 per cent. Beginning with 1929, a distinct improvement occurred. Of 35 patients described, 19 survived, a mortality of 46 per cent. Of the 20 patients who recovered, however, 5 had some residual paralysis. Browder and Meyers<sup>3</sup> followed Van Den Berg's paper with a report of 5 cases of acute metastatic spinal epidural abscess, in 1 of which the patient recovered. The condition in this case, however, represented an extension of osteomyelitis of the rib. During December of the same year, Campbell<sup>4</sup> described 4 cases, with but 1 recovery. The patients in Raney's<sup>5</sup> 3 cases reported in 1939 had pneumococcal infections, and, as with all previous acute pneumococcal epidural abscesses, all of them died. Still later in 1939, Bunch and Madden<sup>6</sup> reported 4 cases of acute metastatic spinal epidural abscess, in 3 of which the patients recovered. Only 1 patient, however, regained complete function, the others remaining paraplegic two and eleven years respectively after laminectomy.

Any improvement in the prognosis of this infrequent infection undoubtedly has depended on earlier diagnosis and operative interven-

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From the Department of Surgery of the University of Southern California.

1 Van Den Berg, W. J. Acute Metastatic Spinal Epidural Abscess, California & West Med **46** 257 (April) 1937

2 Morgagni, J. B. De sedibus et causis morborum, Paris, M. C. Comper jun., 1823

3 Browder, J., and Meyers, R. Infections of the Spinal Epidural Space. An Aspect of Vertebral Osteomyelitis, Am J Surg **37** 4 (July) 1937

4 Campbell, M. M. Pyogenic Infections Within the Vertebral Canal. Bull Neurol Inst New York **6** 574 (Dec) 1937

5 Raney, R. N. Acute (Pneumococcal) Metastatic Spinal Epidural Abscess. Report of Three Cases, Bull Los Angeles Neurol Soc **4** 31 (March) 1939

6 Bunch, G. H., and Madden, L. E. Acute Epidural Abscess with Compression of the Cord, South Surgeon **8** 291 (Aug) 1939

tion With few exceptions, every patient with an undiagnosed epidural abscess untreated by operation has died as have, probably, all patients with epidural abscesses of the acute metastatic type When the diagnosis is made early, before evidence of paralysis has set in, and laminectomy is performed as soon as possible, the chances of recovery are at least somewhat favorable On the other hand, if the diagnosis is established after complete paralysis has set in, not only is the prognosis grave but, should laminectomy lead to recovery and relief of pain, residual paralysis almost always persists

If Van Den Berg's figures are accepted and the 2 cases in the present report are added to those mentioned, some 86 acute metastatic spinal epidural abscesses have been observed, and 26 of the patients have recovered Seven of those who recovered have had some residual paralysis The discrepancy in the number of cases reported is no doubt due to the difficulty of separating the acute from the chronic type and the metastatic type from that occurring by extension from a contiguous infection At all events, the disease continues to be uncommon and the prognosis poor Inasmuch as the patients in the following 2 cases of acute metastatic spinal epidural abscess were operated on prior to paralysis, with complete recovery, and because the cases illustrate some important features in the diagnosis of the condition, it was believed justifiable to describe them

#### REPORT OF CASES

*CASE 1—Acute metastatic lumbar epidural abscess secondary to a furuncle of the left shoulder, infecting organism, Staphylococcus, laminectomy, drainage of the abscess, recovery*

J. M. S., a white youth aged 19, was admitted to the Los Angeles County Hospital Nov. 13, 1939, with a history of furunculosis of the left shoulder occurring a month previously On November 3 he first experienced lumbar pain, which was accentuated by forward movement of the head Shortly afterward he noticed a radicular pain along the left side of the abdomen and found it necessary to walk bent over toward the affected side He also discovered that coughing or straining accentuated the pain He observed no weakness of his extremities and no symptoms referable to the bladder One physician consulted suspected a perinephritic abscess

Because at this time he was a member of a Civilian Conservation Corp camp, he was admitted to the Station Hospital, March Field, Calif., on November 11 At this time his temperature was 99.8 F. Rigidity of the neck and pain in the cervical region were noted, as well as pain and tenderness in the lumbar region The general physical examination disclosed nothing unusual in the heart, lungs or abdomen Except for a positive Kernig sign, neurologic examination revealed nothing noteworthy Clear fluid containing 23 lymphocytes per cubic millimeter was obtained on lumbar puncture A Queckenstedt test was not performed, a notation being made that no manometer was available After the puncture the patient complained of increased headache and pain in the back He was then seen by a county health officer at Riverside, Calif., who made a tentative diagnosis of poliomyelitis and advised transfer to the Los Angeles County Hospital At this time no unusual weakness

or paralysis was described, but the rigidity of the neck and spine was still present, and the Kernig sign was positive. The family and past history were unimportant.

On admission the temperature was 102.4 F, the pulse rate 100 and the respiratory rate 16. The patient was mentally clear but obviously ill. He complained of pain in the left lumbar region and in the left side of the abdomen. Forward movement of the neck produced rigidity in the last 40 degrees of flexion. The Kernig sign was positive. Tenderness was noted in both lumbar regions, particularly on the left. The cranial nerves were intact, the deep reflexes were present, active and equal, and the Babinski sign was negative bilaterally. No sensory loss was noted. At this time the impressions were those of poliomyelitis without paralysis, choriolymphocytic meningitis, osteomyelitis of the lumbar portion of the spine and paravertebral abscess.

The value for hemoglobin on admission was 98 per cent, and the leukocyte count was 24,600 per cubic millimeter of blood, with 72 per cent neutrophils. The Wassermann reaction of the blood was negative. Roentgenograms of the lumbar and thoracic portions of the spine taken on November 16 revealed no destructive lesion. The chest was also essentially normal. A slightly cloudy fluid under 240 mm of pressure and containing 102 cells per cubic millimeter, 90 per cent of which were lymphocytes, was obtained by puncture at the fourth lumbar interspace. The Pandy reaction was positive, the value for total protein was 170 mg per hundred cubic centimeters, and the Wassermann reaction was negative. No Queckenstedt test was performed.

On November 19, a lumbar puncture at the level of the third and fourth interspaces returned frank yellow pus which on smear and culture showed staphylococci. A cisternal puncture revealed clear fluid, with 96 cells per cubic millimeter and no organisms. An abscess on the scalp which had developed at this time also yielded staphylococci on culture. Another lumbar puncture on November 20, returned xanthochromic fluid with a strongly positive reaction for globulin. No Queckenstedt test was done. Culture of the fluid produced staphylococci, and a blood culture on November 21 yielded *Staphylococcus aureus*.

The patient's condition continued to be critical. The leukocyte count was 27,800 per cubic millimeter on November 17 and 24,400 per cubic millimeter on November 21. The impression at this time was that of staphylococcus septicaemia with perinephritic abscess, abscesses of the scalp and abscesses of the lumbar muscle or epidural abscesses. *Staphylococcus bacteriophage* was given in doses of 5 cc. every four hours and increased to 10 and 15 cc each day until the patient's admission to the neurosurgical service, when its use was discontinued.

The patient was seen in neurologic consultation on November 21, at which time marked tenderness over the third and fourth lumbar segments of the spine was noted, with a positive Kernig sign and some stiffness of the neck as well as pain in the lumbar area on flexion. The impression was that of an epidural abscess in the region of the third lumbar segment, without involvement of the nerve. Neurosurgical consultation was then recommended.

When seen by the resident neurosurgeon, on November 22, the patient appeared ill and toxic. A draining occipital furuncle was noted. Stiffness of the neck was evident, and forward flexion produced pain in the lumbar region. On funduscopic examination the margins of the disks were well outlined except for the nasal margin of the left disk, which was moderately blurred. The veins were overfilled. Otherwise the cranial nerves were intact. Examination of the back disclosed marked tenderness from the second lumbar segment to the sacrum, with softness of the paravertebral region bilaterally. No sensory disturbance was noted. Motor power appeared to be intact, but there was so much pain on movement of



the lower extremities that this could not be tested satisfactorily. The impression was that of acute metastatic lumbar epidural abscess.

With the patient under avertin with mylene hydrate and ether anesthesia a lumbar laminectomy was performed on November 23. The second to the fifth lamina inclusive were removed. With exposure of the dura, pockets of thick, yellowish pus were opened from the second to the fifth lumbar segments of the spine, above and below which no evidence of abscess formation was discernible. Penrose drains to the dura were inserted through separate stab wounds on the lateral side of the incision. The wound was then closed with chromic and plain catgut, and the cutaneous incision was loosely closed with interrupted fine black silk sutures. Before this was done, powdered sulfapyridine was placed in the wound. The patient was given a transfusion of 500 cc. of citrated blood.

Because of the history of the lumbar punctures through the involved area and the growth of staphylococci from the first sample of spinal fluid, meningitis was feared as a complication. After the laminectomy the temperature subsided and the patient's general condition was good. Drainage from the operative area continued rather profusely. The drains were removed on the fifth postoperative day. When the skin sutures were taken out on the seventh postoperative day, the edges of the skin separated at the upper portion of the wound, and drainage continued. Sulfapyridine was given until the eleventh postoperative day, when the patient's condition was so much improved that it was no longer indicated.

Although he had some vesical difficulty during the first few days, this subsequently improved and did not recur. His postoperative course was thereafter uneventful, and by the thirty-third postoperative day the wound had approximated except for a few small areas where the epithelial tissue had not closed the gap. During the previous week the patient had been up in a wheel chair.

Films of the chest taken on December 14 showed a few calcified tubercles but no other pathologic change. The patient was discharged from the hospital on January 6, the forty-fourth postoperative day, with no residual paralysis. He has remained well since that time.

*Comment*—The importance of the Quackenstedt test is evident in this case, and had it been employed it might have led to earlier diagnosis and operative intervention. The danger of meningitis following the injudicious use of lumbar puncture in such a case is evident. Rosamond<sup>7</sup> and Mixter and Smithwick<sup>8</sup> each reported a case in which recovery followed the development of such a complication. Most authors agree that packing the wound wide open is the preferable method of drainage and that without such drainage reopening of the wound has been necessary. Although in this case such packing was not carried out and closure for that reason probably took place more rapidly, the former method is undoubtedly safer and is preferable. The use of staphylococcus bacteriophage and sulfapyridine therapy may have been helpful, but this factor is difficult to evaluate.

7 Rosamond, E. Epidural Abscess Complicated by Staphylococcus Meningitis. Report of Case with Complete Recovery Following Operation, *J. Pediat.* **1**: 230 (Aug.) 1932.

8 Mixter, W. J., and Smithwick, R. H. Acute Intraspinal Epidural Abscess, *New England J. Med.* **207**: 126 (July 21) 1932.

CASE 2—*Acute metastatic lumbar epidural abscess secondary to a furuncle of the left cheek, infecting organism, Staph aureus, hemolytic type, laminectomy, drainage of abscess, recovery*

K R, a Syrian boy aged 3½ years, was admitted to the Children's Hospital Dec 12, 1939, with the history of development of a furuncle of the left cheek about two weeks previously. Some two days later he fell on his back, and he complained rather constantly of pain in the lumbar region thereafter. He was taken to his family physician, who obtained normal-appearing roentgenograms of the lumbar region. About three days prior to hospitalization he complained of pain in his left thigh and knee, which seemed to become progressively worse. He kept his left leg flexed. No difficulty with vesical or rectal control was noted. He seemed rather feverish and irritable.

The family history was unimportant except that his mother had died four hours after his birth. His father was living and well. The patient had had no childhood diseases, and his development as recorded was quite normal.

He was seen in neurosurgical consultation on the evening of December 14. He appeared well developed and well nourished. He weighed 35 pounds (15.9 Kg). He was irritable and resented being examined. His temperature was 101 F but had been 104 F on admission. The pulse rate was 140 and the respiratory rate 24. He was clear mentally but obviously ill. Stiffness of the neck was evident on forward movement of the head. The ear drums were intact, as was the nasal septum. Noticeable on the left cheek was a partially healed furuncle. There was no cervical adenopathy, and nothing unusual was discovered in the heart, lungs or abdomen. The left leg remained flexed, and palpation over the lumbar portion of the spine caused considerable pain. No attempt was made to examine the cranial nerves, but from a superficial investigation nothing unusual was discovered. The Kernig sign was strongly positive bilaterally. Because of his irritable condition and the fact that he had been examined several times previously, a complete neurologic examination was not carried out.

Roentgenograms of the lumbodorsal portion of the spine and of the pelvis, taken on admission, showed no pathologic changes. The value for hemoglobin was 65 per cent, the erythrocytes numbered 3,400,000 and the leukocytes 18,650 per cubic centimeters of blood. The urine gave negative reactions for albumin, sugar and acetone, and microscopically no casts or erythrocytes were seen. Wassermann and Kahn tests of the blood on admission gave negative results, and culture of blood taken on December 14 produced no growth after eleven days.

On the afternoon of December 14, Dr G M Jorgenson attempted a lumbar puncture at the level of the third and fourth lumbar interspaces. No fluid was obtained at the fourth interspace, but when the third was punctured 1 cc of thick, yellowish pus was liberated by aspiration, which on smear and culture proved to contain *Staph aureus* of the hemolytic type. In view of the history, examination and results of lumbar puncture the diagnosis of an acute metastatic lumbar epidural abscess was made, and laminectomy was advised.

With the patient under avertin with amylene hydrate and ether anesthesia a lumbar laminectomy with removal of the first to the fifth lumbar lamina inclusive was performed that evening. Thick, yellowish pus was liberated in pockets along the dura from the first lumbar segment of the spine to the upper part of the sacral region. The dura was not torn. Although it was believed that the epidural abscess might have extended a few laminae higher, because of the patient's condition no additional laminae were removed. Material for culture was taken from the epidural abscess and later yielded *Staph aureus* of the hemolytic type.

A large Penrose drain was inserted over the dura and brought out through the lower margin of the wound. The wound was then closed with chromic and plain catgut, and the cutaneous incision was loosely closed with interrupted black silk sutures. Because of the infection, vascularity was more noticeable than usual throughout the procedure. During the operation the child was given a transfusion of 300 cc of citrated blood.

On December 14 the patient was given 5.2 cc of a 30 per cent solution of sodium sulfapyridine intramuscularly, and, with the exception of 3 cc on December 17 and 18 he was given a similar amount daily thereafter until December 19. At this time 7 grains (0.45 Gm.) of sulfapyridine was given four times daily by mouth until December 24, when its use was discontinued. This maintained the level of sulfapyridine between 5 and 8 mg. per hundred centimeters of blood. On December 18 the hemoglobin was 69 per cent, the erythrocyte count was 3,610,000 and the leukocyte count 26,100 per cubic millimeter, with 86 per cent neutrophils. By December 28 the leukocyte count had fallen to 10,800, and by January 3, 1940, to 7,000 per cubic millimeter. At this time the value for hemoglobin was 70 per cent, and the erythrocytes numbered 3,750,000 per cubic millimeter. The patient made a satisfactory recovery without evidence of residual weakness. Because he lived out of the city, he remained in the hospital until the wound closed completely. This occurred on January 24. He has been quite well since that time.

*Comment*—Fortunately, when pus was obtained on lumbar puncture, the diagnosis was suspected and confirmed by laminectomy performed as soon as arrangements could be made. The value of such early diagnosis and laminectomy would again seem indicated.

#### GENERAL COMMENT

*Etiology*—It is generally believed that abscesses of the epidural space occur either by extension from a contiguous infection or by metastasis from a distant focus. The larger group, composed of abscesses of hematogenous origin, is more interesting and presents a more difficult problem in diagnosis.

According to Dandy,<sup>9</sup> the fatty and loose areolar tissue filling the epidural space offers a foothold for current hematogenous infections, and the intraspinal location of these tissues makes trauma an important inciting agent in their development. It is generally believed that the metastasis of the infectious variety is to the epidural fat. On the other hand, Browder and Meyers<sup>3</sup> have expressed the view that the hematogenous variety metastasizes to the vertebrae, whence it spreads into the epidural space. The explanation of localization in the epidural space without similar hematogenous involvement elsewhere and the reason for the infrequent occurrence of such epidural abscesses with furunculosis so common are neither easily explained nor easily understood.

<sup>9</sup> Dandy, W. E. Abscesses and Inflammatory Tumors in the Spinal Epidural Space, *Arch Surg* **13** 477 (Oct.) 1926.

The striking feature about the pathologic picture of such an abscess is that it occurs between the dura and the periosteum of the vertebrae and in practically every case posteriorly. This is explained by the fact that, in accordance with Dandy's<sup>9</sup> studies of the anatomy of the epidural space, the dura divides into two halves at the foramen magnum, the inner half acting as the dura proper and the outer half serving as the periosteum of the vertebrae, with the epidural space between the two. Posteriorly, this space consists of a layer of fat, connective tissue and arterial and venous plexuses. This space is present only dorsal to the nerve attachments, because ventrally the dura is everywhere closely applied to the bones of the vertebrae and their ligaments. Below the second sacral bony segment, however, the epidural space surrounds the dura on all sides. The lumbar and thoracic regions are the most common locations for these abscesses, which is explained by the fact that the space is only potential in the cervical area. Below the seventh cervical vertebra the space gradually deepens, attaining a depth of 0.5 to 0.75 cm. below the fourth and eighth dorsal vertebrae, after which it again tapers and becomes shallow below the eleventh thoracic and the second lumbar vertebrae. Over the remaining lumbar vertebrae and the first and second sacral vertebrae, the epidural space attains its greatest depth.

Interestingly, with few exceptions the pyogenic organism associated with spinal epidural infections has been the staphylococcus. Only rarely has the pneumococcus been the infecting organism, and invariably it has proved fatal.<sup>5</sup> A few cases of streptococcal infections have been described, and Raymond and Sicard<sup>10</sup> reported a case of infection with the typhoid bacillus.

Between the two extremes of the acute and chronic forms of the disease there occurs a wide variation in the amount of pus and granulation tissue present. Pus may be found to extend from the lower cervical to the lumbar region with no granulation tissue evident, while, on the other hand, the granuloma may be the only evidence of a chronic infection. The spinal cord is either normal or edematous in appearance. In some instances the cord shows microscopic changes similar to those produced by experimental pressure myelitis. According to Elsberg and Hassin<sup>11</sup> such changes are not merely pressure degeneration but are the result of local obstruction of the circulation of the cord and toxemia.

10 Raymond, F., and Sicard, J. A. *Épidurite purulente lombaire à bacilles d'Eberthe dans la convalescence d'une fièvre typhoïde, paraplegie, ponction lombaire, laminectomie, guérison*, Bull. et mém. Soc. méd. d. hop. de Paris 22 80, 1905.

11 Elsberg, A. E. *Surgery of the Spinal Cord*, in Nelson, Looser, Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, p. 459. Hassin, G. B. *Circumscribed Suppurative (Non-Tuberculous) Peri-Pachymeningitis. Histopathologic Study of a Case*, Arch. Neurol. & Psychiat. 20 110 (July) 1925.

*Diagnosis*—Although there is variation in the symptoms depending on the location of the abscess, the history in these cases is rather uniform. Usually the story of some previous infection, often furunculosis, can be obtained, and the lesion may exist at the time of onset of the neurologic symptoms, although in most cases it has subsided. Commonly within the first two weeks but at least during the first two or three months after such an infection, the patient complains of a boring pain in the spine, ordinarily limited to an area corresponding to one or two vertebrae. Usually the pain is constant and is accentuated by coughing, straining or any movement of the spine, and frequently it is associated with local tenderness. Localized swelling may or may not be present. Often the disease assumes the character of a severe toxemia, with noticeable malaise and complaints of chilly sensations, headache, generalized myalgia, feverishness and sweating. The temperature may vary between 101 and 104 F and soon establishes a septic curve, with morning remissions. There is also leukocytosis, with a polymorphonuclear leukocyte count of 12,000 to 25,000 per cubic millimeter. Often culture of the blood yields bacteria. Neurologic signs become evident during the appearance of these toxic symptoms. A radicular type of pain resulting from involvement of the dorsal nerve roots by the advancing infectious process is a distinctive symptom at this time. Depending on the segmental location of the abscess, these root pains may radiate from the back to the front of the chest, to the front of the abdomen or around the pelvis and down the thighs. The spine and neck become rigid, and flexion of the neck on the chest is painful. Extreme tenderness of the spinous processes over the affected area as well as spasm of the adjacent muscles of the back is elicited on examination. Stiffness of the neck and bilaterally positive Kernig signs are ordinarily noted. When the abscess is in the lumbar region, the Kernig signs are extreme and the cervical stiffness slight.

Such are the early signs, and, if the condition is untreated, either gradual or sudden evidence of involvement of the cord becomes apparent, with paraplegia, sphincteric disturbance and sensory loss. As the abscess advances up the space, an advance of sensory loss and paralysis will be noted. When the abscess is in the lumbar region paraplegia becomes manifest more slowly than when it is in the dorsal area, because at the higher levels pressure is exerted on the cord, while in the lumbar region pressure is exerted on the cauda equina.

Although they admittedly increase the hazards to the patient, lumbar puncture and a Queckenstedt test are essential to confirm the diagnosis. When the abscess is in the lumbar region, the danger of initiating meningitis by means of spinal puncture is obvious. On the other hand, the lumbar space is over 1 cm in depth and is distended with pus, so

that a routine puncture is apt to enter this space only and evacuate pus. It is generally believed that the danger from a properly performed lumbar puncture is less than that which occurs from a delay in establishing the diagnosis because of fear of producing meningitis. If the possibility of an epidural abscess is unappreciated, a diagnosis of purulent meningitis may be suggested when pus escapes from the needle. A cisternal puncture will dispel any doubt. If the condition is suspected, aspiration should be made on the needle during the puncture. Thoracic epidural abscesses produce early block, and From's syndrome is commonly present.

*Prognosis and Treatment*—As has been emphasized, almost every patient with an undiagnosed and surgically untreated condition of this kind has died. The prognosis depends on early diagnosis, laminectomy and drainage. When these have been achieved, the chances for recovery appear favorable. If the diagnosis is established after paralysis has occurred, not only is the prognosis grave but, should laminectomy lead to recovery and relief of pain, residual paralysis usually persists. Just how much value the use of bacteriophage may have as an additional therapeutic measure remains controversial. In most cases it seems advisable to employ sulfapyridine.

#### SUMMARY AND CONCLUSIONS

Two cases of acute metastatic lumbar epidural abscess with operation before evidence of compression had set in and with complete recovery are reported.

Abscesses of the epidural space are believed to occur either by extension from a contiguous infection or by metastasis from a distant focus. The larger, more interesting group, that of hematogenous origin, presents a more difficult problem in diagnosis. These abscesses almost always occur posteriorly. This is due to the fact that the epidural space is present only dorsally to the nerve attachments, while ventrally the dura is everywhere closely attached to the bones of the vertebrae and their ligaments. The lumbar and thoracic regions are the most common locations for the abscesses, the epidural space being larger in these areas and only potential in the cervical region. With few exceptions the pyogenic organism associated with these infections is the staphylococcus.

Although there is variation in the symptoms, depending on the location of the abscess, the history is rather uniform. Usually the story of some previous infection, such as furunculosis, can be obtained. Commonly within the first few weeks following such an infection the patient complains of a boring pain in the spine, accentuated by straining or movement. The disease assumes the character of a toxemia with fever and hyperleukocytosis. Radicular pain becomes evident the next

and neck are rigid, and the Kernig sign is positive. Extreme tenderness of the spinous processes over the affected area as well as spasm of the adjacent back muscles is elicited on examination. Either gradually or suddenly thereafter, evidence of involvement of the cord becomes apparent, with paraplegia, sphincteric disturbance and sensory loss. A lumbar puncture and a Queckenstedt test are essential to confirm the diagnosis. When the infection is in the lumbar region the spinal puncture is apt to evacuate pus, and care must be taken not to irritate meningitis. The thoracic epidural abscesses produce early block, and Froin's syndrome is commonly present.

With few exceptions every patient with an undiagnosed and surgically untreated abscess of this type has died. The prognosis depends largely on early diagnosis, laminectomy and drainage. If these are achieved the chances for recovery at least are hopeful. Should the diagnosis be established after complete paralysis has set in, laminectomy may lead to recovery and relief of pain but seldom leads to return of function of the affected muscles.

# A SOLUBLE ROD AS AN AID TO VASCULAR ANASTOMOSIS

## AN EXPERIMENTAL STUDY

SIDNEY SMITH M S

CHICAGO

The feasibility of suturing severed blood vessels has been established by the "auto-hetero" and devitalized vascular transplant work of Carrel and Guthrie<sup>1</sup> and has been confirmed by others<sup>2</sup>. However, the Carrel-Guthrie technic of end to end anastomosis presents technical difficulties which have discouraged its use except by the surgeon with special training.

It is evident that intravascular thrombosis is the primary factor to be guarded against in vascular anastomosis. Local thrombosis is accelerated by liberation of thromboplastic substance, which, to a large degree, parallels the amount of real trauma to the intima of vessels. The precautions to be observed, therefore, are 1. Minimize trauma to the vessels, especially to the intima, by delicate handling. 2. Use sutures treated with liquid petrolatum or olive oil (platelets are less apt to stick to oil-soaked sutures),<sup>3</sup> and expose a minimum of the suture material to the blood stream. 3. Minimize constriction of the lumen at the site of suture so that, by Venturi action, an increased number of platelets are not brought in contact with the exposed parts of the sutures.

I have eliminated the three stay sutures and further simplified the technic of Carrel and Guthrie so that I think that it may be applied to relatively small arteries. The technic is based on use of a soluble rod introduced into the lumen of the severed vessel, so that the mechanical form facilitates the proper approximation and suturing of the ends of the vessel, in much the same manner that use of a wooden egg facilitates mending a stocking.

### METHOD OF PRODUCING ROD

Soluble rods of various diameters may be prepared, with observance of strict aseptic precautions, as follows. Dextrose is heated slowly to 160 C. The slightly caramelized liquid is poured (or sucked) into sterile rubber tubes ranging in

1 Carrel, A., and Guthrie, C. C. Surg., Gynec. & Obst. **11** 266, 1906

2 Klotz, O., Permar, H. H., and Guthrie, C. C. Ann Surg **78** 305, 1923  
Guthrie, C. C. End-Results of Arterial Restitution with Devitalized Fissure  
J. A. M. A. **73** 186-187 (July 19) 1919

3 Markowitz, J. Textbook of Experimental Surgery, Baltimore, Williams & Wood & Company, 1937, p. 396



inside diameter from 2 mm to 3 mm. The filled tubes are then cut into segments 3 cm long. These segments are dropped into ether for a few minutes. The rubber softens and swells, permitting the dextrose rod to be slipped out of the rubber mold with ease. The rods are then coated with some substance that will serve to protect the intima from the dehydrating action of the dextrose. Such a substance may be gelatin (3 per cent solution) or an oil which is liquid at body temperature. If gelatin is used, it must be made up in a solvent which is relatively nonsolvent for dextrose. Dodecyl alcohol serves this purpose.

The rods may be fastened to needles which serve as handles and dipped repeatedly into warm, sterile gelatin solution until a fairly uniform coating of gelatin is obtained. The rods are then fastened by means of the handle of the needle to a sterile cork plate in a vacuum desiccator. A partial vacuum is created. The gelatin coat dries in two to three days.

An alternate and simpler method, more recently used, is to coat the rods with an oil which, in the amounts used (0.02 cc), probably presents no practical dangers from oil emboli. For this purpose theobroma oil U S P (cocoa butter) is blended with some other fat, with wax or with paraffin (with a higher melting point). Theobroma oil U S P (75 per cent) and paraffin (25 per cent) (by volume) produces a blend which liquefies at body temperature. The rods are dipped into sterile solution once, fastened immediately to a sterile cork plate in a desiccator and stored until used.

#### TECHNIC OF BLOOD VESSEL SUTURE BY AID OF SOLUBLE ROD

The vessel to be sutured is isolated from the surrounding tissue by packs moistened with warm physiologic solution of sodium chloride. The adventitial coat is stripped back from each end of the artery for a distance of 1 cm. The lumen is washed out with physiologic solution of sodium chloride and then with olive oil.

The continuous suture technic is used. After the first suture is placed but before it is tied, the soluble rod, corresponding in diameter to the lumen of the flaccid vessel, is inserted one-half its length into one end of the artery. As the suture is being drawn tight preparatory to tying, the other end of the artery is worked over the protruding half of the soluble rod. The suture is then tied. The free end of the thread is trimmed off, and the continuous "over and over" suture completes the anastomosis. The continuous sutures are placed 1 mm apart and 1 mm or less from the ends of the artery. Mild tension is maintained on the thread during this process in order to prevent the sutures from loosening between each sewing maneuver. The site of the anastomosis is then held lightly between the thumb and the index finger while the proximal clamp is removed. The rod goes into solution in the pulsating blood in one minute or less. The peripheral clamp is then removed, reestablishing the circulation. Some slight oozing of blood from the suture holes and from the area between the sutures occurs immediately on release of the clamps, but this bleeding subsides within a minute or two. Pronounced bleeding caused by two sutures inadvertently placed too far apart may be controlled by addition of a single interrupted suture.

After the oozing has completely stopped, permanent reenforcement is obtained by suturing the arterial sheath securely around the artery at the site of the anastomosis. Fifty-five experiments on 33 dogs were done. Obviously, in developing the technic, failure due to the composition of the rod and failure due to faulty surgical technic must be considered. However, after the technic had been established a high percentage of success was realized.

#### DESCRIPTION

The following description is based on observations of the last eight consecutive operations performed, using the carotid arteries of dogs ranging from a dog weighing 15 pounds (6.8 Kg) to a dog weighing 60 pounds (27.2 Kg). The average weight was 30 pounds (13.6 Kg). There was one failure (due to an occluding thrombus adherent to the suture line) in the case of a dog weighing 35 pounds (15.9 Kg). The remaining 7 experiments, or 86.5 per cent, were successful. The examinations consisted of making an exploratory incision under sterile precautions at the site of the anastomosis one week after operation to determine the functional patency of the vessel. A second observation followed from two weeks to a month later, at which time the animal was killed and sections of the artery were taken for histologic study.

#### OBSERVATIONS AT EXPLORATORY OPERATION

At the site of the anastomosis, that part of the fascial sheath which was sutured around the artery had in every instance become fused to the artery and was highly vascularized. The vessel was patent and functioning as determined by palpation. There were no instances of leakage, hematomas, loose sutures or other evidence of degeneration or breakdown of the conduit. The vessel was pliable at the final examination. When the vessel was opened at postmortem examination, the internal wall was glistening and healthy in appearance. The sutures were covered with a semitransparent glistening membrane continuous with the glistening internal wall of the vessel. There was no evidence of constriction, dilatation or sacculation. In only 1 instance was there a small but organized thrombus, which measured about 0.3 mm in diameter.

#### MICROSCOPIC EXAMINATION

The endothelium had proliferated across and covered the sutures and the line of anastomosis. The endothelium was slightly thickened at the site of anastomosis but was essentially normal. There was no evidence of intimal injury caused by the dextrose rod. The silk sutures were encapsulated and surrounded by a few foreign body cells. The muscle fibers of the media injured by the sutures were in the process

of repair or were completely repaired by fibroblastic connective tissue. The adventitial layer had fused to the highly vascularized fascial sheath. Essentially, from the functional standpoint and excepting the encapsulated sutures, the histologic picture was that of an artery which has never been operated on.

#### COMMENT

Although many failures occurred during the developmental stage of the technic, it is considered significant that once the technic was established, a high percentage of successes was realized. Long term studies were not undertaken, because the work of Carrel and Guthrie<sup>1</sup> adequately established the fact that once the thrombosis at the suture site is eliminated by endothelialization of the suture line, the sutured artery is subject to the usual functional history of the rest of the arterial system of the animal.

#### SUMMARY

A new technic for simplifying vascular anastomosis is described in which a soluble rod is introduced into the vessel to supply mechanical form and support during the suturing process.

The soluble rod dissolves promptly (in one minute or less) in the blood stream after the circulation is reconstituted.

Directions for preparing and storing these soluble rods are given.

The modified Carrel and Guthrie technic of blood vessel anastomosis with the aid of the soluble rod is described.

Histologic studies reveal no injuries of the intima attributable to the dextrose rod.

It is concluded that the soluble dextrose rod, covered with a thin film of oil or gelatin, is a practical aid in vascular anastomosis.

Dr. A. J. Carlson, of the University of Chicago, and Dr. Willis Potts, of Rush Medical College, gave assistance and criticism in this study. Mr. Edwin Smith assisted in the experimental operations.

# ACUTE PANCREATITIS

AN ETIOLOGIC REVIEW AND REPORT OF THIRTY-FIVE CASES

EDWARD F LEWISON, M D \*

BALTIMORE

Sir Thomas Watson (1843), in one of his scholarly lectures, commented "It may seem a slight to the pancreas to pass it over without noticing the diseases to which it is subject. But really these diseases appear to be but few, and they do not signify their existence by any plain or intelligible signs." In point of occurrence, acute pancreatitis is sufficiently uncommon to suffer from diagnostic imprudence, yet sufficiently common to warrant the utmost diagnostic solicitude. At the Beth Israel Hospital between 1921 and 1939 there have been just over 100,000 admissions. Of this number, 33 were for acute pancreatitis, representing an incidence of 1 in every 3,000. This figure is similar to the incidence reported by other American investigators and roughly corresponds to the records of the Leeds General Infirmary in England, reported by Chamberlain (1927). Acute pancreatitis is undoubtedly, then, a rare but dangerous disease, and the widespread interest in this subject can hardly be explained by the statistical incidence. There is an ever increasing school of thought, however, which believes that acute pancreatitis is more *chatoyant* and perhaps milder and more prevalent, frequently masquerading as biliary colic, indigestion or peptic ulcer. This trend of thought is persuasive, and if the assumption is true it is necessary to discipline carefully the laboratory and diagnostic data and in so doing provide the means for a more consistently correct diagnosis. Sir Archibald Garrod's aphorism (1920) that "the more constantly we bear the pancreas in mind as a possible seat of origin of obscure abdominal troubles the less likely shall we be to overlook its lesions" is especially true of acute pancreatitis.

In this investigation of 35 cases of acute pancreatitis, one of the members of the surgical staff gave me access to his personal records for the histories of 2 patients who were treated surgically elsewhere.

This report has been restricted to those cases in which the diagnosis of acute pancreatitis has been either established or confirmed by operative examination. No cases of manifest chronic pancreatitis or of acute pancreatitis secondary to an unmistakable primary process elsewhere

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\* Formerly Fellow in Surgery, Beth Israel Hospital New York

have been included. Acute pancreatitis resulting from perforation of a peptic ulcer into the parenchyma of the pancreas has been precluded from this study. Records of pancreatic calculi have also been ruled out. It has been found necessary at times to set up arbitrary standards of classification, but whenever possible the surgeon's note has been adhered to closely.

The diagnostic difficulties associated with this disease are clearly evident in these 35 cases, in which the preoperative diagnosis was found to be correct in 11 per cent of the cases in which it was made without reservation. Acute pancreatitis, however, was considered as an alternative diagnosis in an additional 6 cases, resulting in a partially correct reckoning in 17 per cent. This diagnostic error implies no lack of skill or acumen on the part of the sponsors of these opinions but is rather a reflection on the deceptive nature of the disease and perhaps on the loose liaison between certain clinical principles and helpful laboratory data; namely, determinations of the enzyme content of the blood and of the urine. Of these, estimation of the content of blood amylase and lipase has been recently reemphasized as a valuable, rapid and reliable diagnostic aid when used within its limitations.

This lack of diagnostic uniformity finds ample vindication in the writings of most investigators. Von Schmieden and Schenning (1927), in reviewing 1,510 cases in their collected series, found that a correct diagnosis was made in only 21.8 per cent and a suspected or alternative diagnosis in an additional 17.5 per cent. McWhorter (1932), in reporting 64 cases collected from the records of members of the Chicago Surgical Society, found that a correct diagnosis was made in only 12 per cent. Similarly, more recent authors have found the diagnosis proportionately elusive. Confusion with diseases of the gallbladder was frequent in this series of cases, as well as in the reported observations elsewhere. This is indeed a challenge to diagnostic precision in handling a disease associated with such an appalling mortality and must certainly stimulate interest in all of the complex factors of this perplexing problem.

#### PATHOGENESIS

The protean manifestations of acute pancreatitis are best explained, at least in part, by the varied factors in the pathogenesis of the disease. Despite the general attention that it has attracted, the nature and cause of this lesion remain doubtful. There exists an extensive experimental and clinical literature concerning the manner of origin of acute pancreatitis, and some believe that operation is only a fairly adequate type of treatment. Dragstedt, Haymond and Ellis (1934) suggested that "it is possible that the limit has been reached in the way of operative procedure, and that a further lowering of the excessive mortality must come from

another direction. The fact that the pancreas is an organ indispensable to life, the fact that it is situated in the upper part of the abdomen in close proximity to the extensive celiac nerve plexus, and the fact that it is in a region where the absorption of toxic chemical products occurs with unusual facility operate to limit the scope of surgical treatment."

Many classifications of acute pancreatitis have been described since the first was proposed by Reginald Fitz in 1889. Before him, Klebs (1870) had recognized acute pancreatitis as a cause of "fulminant death" and stressed its pathologic importance. Claude Bernard (1856) reported the production of experimental acute pancreatitis and the early death of the animals following the injection of bile and olive oil into the pancreatic duct. Rokitsansky (1863) carefully recorded the pathologic appearance of acute pancreatitis, and in his textbook on pathology these observations were available to Friedreich (1878), who later published the first well defined and complete description of this disease.

At the turn of the century medical interest seemed focused on diseases of the pancreas. The history and development of knowledge of pancreatitis at that time can be traced in the detailed and comprehensive monographs of Korte (1898), Oser (1898), Mayo-Robson and Moynihan (1903) and Opie (1903). The now famous necropsy of Opie (1901), in which he first described the presence of an impacted stone at the ampulla of Vater and carefully pointed out its relation to acute pancreatitis, is legendary in the annals of medical history. Later, Brocq (1926), in a distinguished paper, divided pancreatitis into two types (1) noninfected and (2) infected. Acute hemorrhagic, acute edematous and subacute manifestations of the disease were considered types of noninfected pancreatitis. The gangrenous and suppurative manifestations were considered types of infected pancreatitis.

The term pancreatitis is in itself misleading, as the appearance of the pancreas is hardly similar to the gross or microscopic changes characteristic of inflammatory lesions elsewhere in the body. Acute pancreatic necrosis is, indeed, a more accurate and descriptive designation, but time-honored precedent makes it difficult to impeach so well established a term as pancreatitis. In this paper the two terms will be used interchangeably.

#### ETIOLOGIC CLASSIFICATION

McWhorter (1932) suggested a useful classification of acute pancreatitis on an etiologic basis. With minor modifications this classification has been followed in this investigation.

##### A Infectious origin

- 1 Invasion of the pancreas along the lymphatics
- 2 Invasion of the pancreas from the blood stream
- 3 Infection by extension along the pancreatic ducts from the duct<sup>1</sup> or from the bile ducts

- 4 Infection by direct extension from infected foci
  - 5 Infection following activation of bacteria and their toxins in the normal gland
  - 6 Infection by bacterial invasion from adjacent altered viscera
- B Noninfectious origin
- 1 Mechanical or obstructive
    - (a) Stone in the common duct or in the ampulla of Vater
    - (b) Spasm of the sphincter of Oddi
    - (c) Edematous occlusion of the ampulla of Vater
    - (d) Metaplasia of the epithelium of the pancreatic duct
  - 2 Chemical, activated pancreatic ferments resulting from
    - (a) Reflux of bile
    - (b) Reflux of duodenal contents
    - (c) Autolysis
  - 3 Degenerative changes in the pancreas
    - (a) Changes secondary to benign or malignant tumors
    - (b) Changes resulting from vascular degeneration or hemorrhage
  - 4 Trauma
- C A combination of two or more factors

In following this orderly outline of the factors concerned in the pathogenesis of acute pancreatic necrosis, no attempt has been made to consider them separately or in the order of their importance. In fact, as will be seen by their intimate coexistence, it is often impossible to single out the factors of major significance in an individual case.

#### A ACUTE PANCREATITIS OF INFECTIOUS ORIGIN

The influence of bacteria as a likely agent in the production of acute pancreatitis has been supported by considerable clinical and experimental evidence. Evaluation of this evidence, however, is difficult, and conclusions drawn therefrom are consequently dangerous. Von Schmieden and Sebening (1927) found bacteria present in the peritoneal exudate in 103 cases of acute pancreatic necrosis and absent in the peritoneal exudate in 84 similar cases. Cultures of the bile yielded bacteria in 54 cases and were sterile in 40 cases of acute pancreatic necrosis. Rehfuess and Nelson (1935), in reporting a collected series of 4,395 cases of acute and chronic cholecystitis, found bacteria present in the wall of the gallbladder in 60 per cent of 1,306 cases and observed "positive bile cultures" in 30 per cent of 1,249 cases. Yet, despite the evident presence of bacteria in the biliary tract in these cases of cholecystitis, associated acute pancreatitis was not noted. Truhart (1902) found bacteria present in the peritoneal fluid, the parenchyma of the pancreas or the foci of fat necroses in 37 of 80 collected cases of acute pancreatitis. In the remaining 43 cases all cultures were sterile. However, bacteria have been shown to be present in the uncontaminated pancreas of the normal experimental animal, and it is likely that a similar situation may exist in man. Tower (1926) found

positive bacterial cultures in 15 of 16 pancreatic biopsy specimens from normal dogs. Bacteria were also regularly observed at autopsy in the peritoneal cavities of dogs subsequent to ligation of the blood vessels supplying the pancreas. These results have been substantiated by Dragstedt (1934) in a group of similar experiments, and he noted, rather surprisingly, that "all cultures taken from the necrosing pancreatic tissue of the dogs that died from autolysis of the pancreas yielded an organism very similar to, if not identical with, *Cl. welchii*." The predominance of this organism is not corroborated by the bacteriologic studies made in the operating room or at necropsy but, as has been suggested by Dragstedt, may be accounted for by its capacity to overgrow other organisms.

Careful bacteriologic studies of acute pancreatic necrosis are singularly meager, but in those reported colon bacilli, staphylococci and streptococci have been the organisms most frequently cultured. Perhaps the anaerobic bacteria are seldom found because seldom looked for, but even the prevalent *Clostridium welchii*, when specifically sought, is rarely cultured in cases of this disease.

In the series reported in this paper it is interesting to note that in case 35 there was a growth of hemolytic *Staphylococcus albus* in all of four separate cultures, the material for which was taken at operation from the gallbladder bile, the wall of the gallbladder, the common duct bile and (by aspiration) the pancreas. Bacterial stains of material from a cystic lymph node revealed no bacteria. The patient showed no postoperative evidence of infection or suppuration and had a rather uncomplicated convalescence. The remainder of the cases were not routinely investigated, and the sporadic cultures that were made were for the most part sterile.

Flexner (1900) carried out a large group of successful experiments in which he was able to produce hemorrhagic lesions in the pancreas by injecting, among other things, bacterial suspensions directly into the pancreatic duct. Hlava (1898) demonstrated a similar lesion but concluded that the hemorrhage and necrosis were not primarily the result of bacterial action.

Bacterial invasion of the pancreas along the lymphatics was first suggested by Klippel and Lefas (1899) as a likely cause of acute pancreatic necrosis. Maugeret (1908) devoted her thesis for the doctorate of medicine to the subject and attempted to produce experimental, clinical and anatomic evidence in support of this mode of pathogenesis. The work of earlier investigators, Sappey (1885), Hoggan (1880), Cullen (1903) and others, had demonstrated the free lymphatic communication between the biliary tract and the pancreas. Franke (1911), by injecting the lymphatics of the gallbladder with dyes, was able to trace the course to the celiac lymph glands and the lymph channels about the



of the pancreas. However, he did not demonstrate that the injected material entered the substance of the pancreas. The concept of the lymphogenous route of infection by extension from the gallbladder to the pancreas was given authoritative credence by Deaver (1921), Judd (1921), Arnsperger (1911) and, for a time, Graham (1922). From the experimental indications of the work of Kodama (1926), Graham (1928) modified his earlier conclusions to conform with the evidence that there is no direct lymphatic communication between the gallbladder and the parenchyma of the pancreas. Clinically Deaver (1921) frequently found in his cases of disease of the gallbladder peripancreatitis with associated lymphangitis and lymphadenitis of the pancreas.

More recently, however, Kaufmann (1927) and Wangensteen (1931) have given convincing and rather conclusive evidence that acute pancreatitis is not propagated from the gallbladder to the pancreas through the lymphatics. Wangensteen (1931) was unable to produce acute pancreatitis in dogs by the germination of an acute biliary tract infection. Even direct injection of bacteria into the parenchyma of the pancreas failed to result in acute pancreatitis. Kaufmann (1927) demonstrated that after an acute infection of the gallbladder produced in experimental animals it was not uncommon to find bacteria present in the pancreas, but bacteria could also be found as a result of bacteremia in the tissues of most of the organs of the body. No pathologic evidence to suggest the presence of acute pancreatic necrosis was found in the animals.

Clinically acute pancreatitis seldom follows fulminant hyperacute cholecystitis but is more commonly associated with chronic cholecystitis. Yet, if the lymphatic spread of infection from the gallbladder is of singular significance in the causation of acute pancreatitis, one would expect to find the acute phase of these diseases a concomitant occurrence of far greater frequency.

Bacterial invasion of the pancreas from the blood stream may produce acute pancreatic necrosis on rare occasions, either by metastatic foci in the presence of pyemia or by extension of infectious thrombophlebitis. Experimentally, Rosenow (1921) found that streptococci isolated from the tonsillar crypts of patients who were suffering from disease of the biliary tract had an elective affinity for the gallbladder and pancreas when intravenously injected into animals. Streptococci of unrelated strains showed no such localization. Kaufmann (1927), however, injected bacteria directly into the portal vein and found that a generalized bacteremia resulted in which the organisms could be isolated from the pancreas and from almost all of the other body tissues as well. Microscopic sections of the pancreas revealed low grade perivascular round cell infiltration.

Blood-borne metastatic lesions complicating mumps have been observed by investigators for many years. Brahdry and Scheffer (1931) reported 156 cases of clinically suggestive acute pancreatitis untreated by operation in 8,306 cases of epidemic parotitis. Patients with mumps most often exemplify the acute edematous type of pancreatitis, and the transient attack may be of minor significance. Two reported autopsies confirmed the association of acute pancreatitis and mumps, and an edematous, congested and enlarged pancreas was observed in both cases. In 1 of them the pancreatitis was a contributory factor to acute nephritis and pulmonary congestion. Farnam (1922) reported a case of acute pancreatitis following mumps in which the condition was treated surgically. *Streptococcus viridans* was isolated from the peritoneal exudate. Hematogenous acute pancreatitis secondary to an acute infectious disease, such as typhoid fever, scarlet fever or diphtheria, is a rare complication and usually results in suppurative pancreatitis. The clinical character of this type of pancreatic lesion is frequently less severe than that of the hemorrhagic or the necrotic type, and the prognosis is distinctly more hopeful. Acute pancreatitis resulting from bacterial invasion by an infective thrombus or from lodgment of an embolus is most infrequent, but when it is recognized the pancreas is found to be the site of either single or multiple abscesses. Douglas (1935) discussed a case of multiple pancreatic abscesses following suppurative portal phlebitis but noted absence of the clinical signs and symptoms suggestive of acute pancreatitis.

In a careful examination of the 35 case histories presented in this report only 3 patients were found to have had an infection of the upper respiratory tract immediately prior to the onset of acute pancreatitis. No further evidence to incriminate the more obvious foci of infection could be uncovered from these records or from the protocols of other investigators.

A history of alcoholism, acute or chronic, was either not mentioned or not present in the records of all of the cases in this series. Wenner and Tennant (1938), in reviewing 4,000 autopsies performed at the New Haven Hospital, found acute pancreatitis in 66 per cent of 38 cases associated with alcoholism, and, conversely, in 53 per cent of the cases of acute alcoholism this condition was associated with acute pancreatitis. The mode of action of alcohol in its relation to acute pancreatitis remains speculative, however, the authors mentioned several interesting physiologic considerations. The role of alcohol alone must certainly be a insignificant one, considering the almost universal use of this substance, yet the association of alcohol with one or more ancillary factors probably serves as a positive etiologic agent in a limited group of cases in which acute pancreatic necrosis develops.

Bacterial extension along the pancreatic ducts from either the duodenum or the bile ducts has often been shown experimentally to be an inciting agent in the causation of acute pancreatitis. Egdahl (1907) noted clinically that in 32 of 105 cases of acute pancreatitis there were associated gastrointestinal disturbances which could be directly invoked in a causal relation. Alcoholic duodenitis was said to be present in 17 of these cases. It is rather difficult to determine the manner of origin of these pancreatic lesions, although it has been suggested that they occur either by penetration of altered duodenal contents into the pancreatic ducts or by direct extension through the intestinal wall. Hess (1905) suggested that antiperistaltic movements of the intestine, which are frequently associated with enteritis, may aid in forcing gastric or duodenal contents into the pancreatic ducts. Anatomic evidence fails to support this point of view. Regurgitation of duodenal contents is prevented by the oblique, valvelike entrance of the ampulla of Vater, which under increased intraduodenal pressure serves to close the ampulla more effectively and prevent reflux. It is true, however, that an anomalous or patulous papilla of Vater can produce a functional change sufficient to explain the occurrence of acute pancreatitis in rare cases. Most experimental attempts to allure duodenal contents into the pancreatic ducts have been unsuccessful. Seidel (1910) established low duodenal obstruction followed by stasis, regurgitation and so-called acute pancreatic necrosis, but Dragstedt (1934) has challenged the evidence obtained in this experiment as incorrectly interpreted.

Von Schmieden and Sebening (1927) have collected 50 cases of invasion of the duct of Wirsung by ascarides with resultant acute pancreatic necrosis. This demonstration of the penetration of duodenal contents in the form of a round worm into the pancreatic duct is virtually self-evident proof that in certain cases acute pancreatic necrosis may be attributed to infection and irritation by this route.

Direct extension from infected foci has been held responsible for many lesions of the pancreas. In innumerable cases so-called acute pancreatitis has been reported as resulting from penetration of a duodenal ulcer into the pancreatic parenchyma. The pathologic mechanism of this process remains obscure, yet it is confidently regarded by some as a contiguous spread of infection from the adjacent gastrointestinal tract.

The activation of bacteria thought to be normally present in the pancreas has been given but passing consideration as a likely cause of acute pancreatitis. However, Andrews, Rewbridge and Hrdina (1931) offered some vindication for this idea by investigating the role of *C. welchii* in producing intraperitoneal inflammatory lesions. Using dogs, they concluded that the action of bile presumably aids in permitting local tissue permeability by *C. welchii*. This organism has also been

shown to produce a powerful hemolysin, but there is no present evidence to relate this toxin to the hemorrhage and necrosis associated with acute pancreatitis. The presence of bacteria within the parenchyma of the pancreas may yet prove to be an important factor in the pathogenesis of this disease. Dragstedt (1934) and his associates have demonstrated the role of bacteria in enhancing the proteolytic power of the enzyme trypsin. The split protein end products of this reaction, liberated within the pancreas and readily absorbed, may be directly responsible for the marked degree of toxemia exhibited by patients with acute pancreatitis.

Bacterial permeability of an inflamed hollow viscus may occur late in the disease, even without perforation. This has been demonstrated clinically in cases of typhoid fever with resultant localized or generalized peritonitis. Should the peritoneal inflammation occur in the region of the pancreas, fulminant acute pancreatitis may terminally confuse and "climax" such a disease. McClure (1907), however, was unable to confirm the results of earlier investigators regarding bacterial permeability in cases of acute intestinal obstruction. He found that permeability occurs, if at all, very late in the course of mechanical ileus and thus can hardly be the source of a pancreatic infection.

#### B ACUTE PANCREATITIS OF NONINFECTIOUS ORIGIN

The theory of mechanical obstruction in the ampulla of Vater, resulting in a common channel between the ductus choledochus and the main pancreatic duct, was first verified as a cause of acute pancreatitis by Opie (1901). The mechanism of the reflux of bile into the pancreatic duct through the agency of an impacted gallstone in the ampulla of Vater is directly dependent on several fundamental considerations. First, the anatomic junction of the ducts at their entrance into the papilla of Vater must be so arranged as to allow their conversion into a functioning common channel by the presence of any one of the following: (1) a small calculus, (2) biliary dyskinesia or (3) acute edema of the ampulla of Vater. Second, granted the formation of a common channel, it is necessary to learn the relative ductal pressures to determine competently in which direction the secretions will flow.

To ascertain these facts, Opie (1903) measured the diverticulum of Vater in 100 specimens and found 89 instances in which the two ducts joined to form a common opening. Of these, there were 30 in which the length of the diverticulum was greater than 0.5 cm and 21 in which the diameter of the diverticulum was greater than its length, thus making partial occlusion of the orifice by a spherical stone obviously impossible. Baldwin (1911) observed a common entrance of the ducts in 78 per cent of 90 cases, and Ruge (1908) observed it in 75 per cent of 43 cases, but Mann and Giordano (1923), working with 200 cases,

specimens, concluded that in only 35 per cent of the cases did the junction of the ducts permit development of a common channel by obstruction at the papilla. Cameron and Noble (1924), however, introduced a small biliary stone into the ampulla of Vater in fresh autopsy specimens and, by forcing fluid into the hepatic duct at a low pressure, noted that a reflux of bile into the pancreatic duct can anatomically occur in 66 per cent of normal specimens.

The literature records more than a few cases of acute pancreatitis in which either the ducts had a separate duodenal opening or the duct of Santorini drained the major portion of the gland. Under such circumstances the theory of the common channel offers no causal solution for acute pancreatitis, and other factors must best explain the pathogenesis in these cases. Thus, although evidence regarding the anatomic plausibility of the theory of a common channel is conflicting, it is probable that in about half of all normal persons the morphologic structure of the biliary tract is such that a small gallstone might divert the bile into the pancreatic duct.

Archibald (1919) has experimentally supported the belief that biliary dyskinesia may convert the ducts into a common channel and that the sphincter of Oddi can withstand a pressure sufficient to allow reflux of bile into the pancreatic duct. Animals under anesthesia were used in his work, but, more recently, confirmatory clinical evidence has accumulated to substantiate this visceral neuromuscular imbalance in man. Wangensteen (1931) and his associates, using cats, mechanically closed the ampulla of Vater with a suture and noted the reflux of bile into the pancreatic duct by contraction of the gallbladder. This produced acute pancreatitis in 50 per cent of the animals. However, they were unable to demonstrate any retrojection of bile without a mechanical obstruction at the papilla. Wangensteen then concluded that the "possibility for such a reflux, however, obtains in a large percentage of persons, and it is possible that such a reflux may be conditioned through a disturbance in the sphincter-regulating mechanism at the ampulla. The actual occurrence of pancreatic necrosis through such an agency in man, however, remains to be demonstrated."

Reflux into the duct of Wirsung has recently been shown to occur during cholangiographic procedures in about 25 per cent of the cases. This is not dependent on a stone at the ampulla but probably more often is due to spasm of the sphincter of Oddi. Yet Boyden (1937) has offered substantial anatomic evidence to show that closure of the pancreatic duct is accomplished primarily through the layer of circular muscle which is common to both bile and pancreatic ducts. The production of a common channel by spasm of the sphincter of Oddi would thus appear to be anatomically improbable even if physiologically possible. An apparent common channel was clinically demonstrated in

case 9 of the present series, in which a bile-stained pancreas was observed at operation. A biopsy specimen taken at the time failed to reveal biliary constituents within the pancreas.

In 1903 Wiener suggested that edema of the ampulla of Vater might so deform its natural structure as to produce a common channel for pancreatic retrojection. Balo and Ballon (1929) supported the possibility of such an occurrence and suggested that it might exist in association with acute or chronic disease of the biliary tract. In their examination of autopsy material they noted evidence of pancreatic retention due to obstruction at the ampulla of Vater. This obstruction was the result of the traumatic passage of a stone associated with an edematous occlusion or a late stricture or possibly the result of a localized inflammation. In a group of unpublished studies on serum amylase which is now in progress I have been able tentatively to confirm this evidence of edematous obstruction and have correlated the results with operative or postmortem observations whenever possible. The presence of a T tube draining the choledochus or the passage of a stone can so impinge on the pancreatic duct or (by edema) occlude it that the altered level of serum amylase will reflect the amount of obstruction of the pancreatic duct.

Should the anatomic arrangement be such as to permit a common channel between the bile and pancreatic ducts, the direction of the secretory flow would, at least theoretically, depend on the individual intraductal pressures. Wolfer (1931) demonstrated that the secretory pressure of the pancreas is greater than that of the liver and gallbladder. This relation has been confirmed by Dragstedt (1934) and his associates. However, Dragstedt concluded that the free intraglandular anastomoses between the ducts of Wirsung and Santorini, as demonstrated by Opie (1903), "make the secretory pressure of the pancreas ineffectual in the majority of cases." The presence of bile and gallstones in the dilated pancreatic duct in a case of acute pancreatitis reported by Robins (1936) corroborates the data in case 9 of the present series and would appear to establish the clinical possibility of the occurrence of pancreatic reflux.

In a facile and instructive study, Rich and Duff (1936), believing that the cause of acute pancreatic necrosis could be found intrinsically within the pancreas, carefully examined the microscopic sections of 150 consecutive autopsies. Metaplasia of the pancreatic ducts was observed in 28.6 per cent of the routine sections examined. In case of acute pancreatic necrosis, however, the routine sections yielded manifest ductal metaplasia in 55 per cent of the cases. From this it was contended that metaplasia of the pancreatic ducts could cause their secretory obstruction resulting, in turn, in a back pressure rupture of the ductal-acinar system of the pancreas. Trypsin, thus liberated,

within the parenchyma of the gland, would then proceed to necrose the surrounding tissue and vessel walls and, by enzymatic destruction, cause acute hemorrhagic pancreatitis. The activation of trypsinogen to trypsin was felt to be unnecessary, as similar vascular necroses could be experimentally produced by injection of purified trypsin.

Yotuyanagi (1937), on the contrary, in an exhaustive study of pancreatic metaplasia, found that it occurred normally in the human being in at least 64 per cent of the specimens which he examined. The metaplasia was a genuine epithelial proliferation, and he suggested a causal relation to vitamin A deficiency or, perhaps, local ductal stasis and irritation. This conspicuous frequency of ductal metaplasia in the normal pancreas is inconsistent with the infrequency of acute pancreatic necrosis and would appear to conflict with the major premise of Rich and Duff.

TABLE 1—*Reported Incidence of Disease of the Biliary Tract Associated with Acute Pancreatitis*

	Cases of Acute Pancrea- titis	Asso- ciated Chronic Chole- cystitis, per Cent	Asso- ciated Acute Chole- cystitis per Cent	Asso- ciated Chole- lithiasis per Cent	Asso- ciated Chole- docho- lithiasis, per Cent	Asso- ciated Ampullary Stones, per Cent	Normal Gall bladder per Cent
Schmieden and Sebening (1927)	Col- lected 1,278 per sonal, 38			Col- lected 70 per sonal, 81	Col- lected, 136 per sonal, 40	Col- lected 44 per sonal, 20	
Guleke (1924)	437			59	5	14	
Egdahl (1907)	105			42			
Fallis and Plain (1930)	26	57.7	15.4	60	8	4	26.9
McWhorter (1932)	64	33	22	40	8	3	39
Present series	35	70	3	80	9	3	20

The importance of the reflux theory of the causation of acute pancreatitis is amplified by a consideration of the relation between chronic cholecystitis, cholelithiasis and acute pancreatitis. Many years ago Korte (1898), Oser (1898) and Opie (1903) all called attention to the frequent association of acute pancreatitis with chronic disease of the gallbladder. Table 1, showing the statistical frequency as collected from the literature, probably represents a certain underestimation, as the contents of the gallbladder and the biliary tract were doubtless overlooked in many instances. These figures are so striking in bearing out the fact that the pathogenesis of acute pancreatitis is intimately related to biliary tract disease that additional clinical corroboration is scarcely needed. In case 15 of the present series the gallbladder was removed eleven years before the development of acute pancreatic necrosis, yet it is difficult to be certain that the pancreatic lesion was not a residue

of earlier cholecystitis. Many similar instances of persistent disease of the biliary tract have been reported in the literature. As Wangensteen (1931) has pointed out, the common denominator in the pathogenesis of acute pancreatic necrosis is the overwhelming preponderance of associated disease of the biliary tract. Whether the mechanism of disease of the gallbladder predisposes to pancreatitis by way of infection, reflux of bile or both remains uncertain, but these facts must now be considered in the light of newer experimental evidence ascribing importance to enzymatic autolysis of the pancreas.

Experiments repeated over a period of many years by many investigators have shown that a great variety of irritating substances will cause acute pancreatic necrosis when injected into the pancreatic duct. The injection of bland substances, as was shown by Flexner and Pearce (1901) and Guleke (1904 and 1908) will not produce such necrosis. The careful work of Flexner (1906) demonstrated that the power of bile to cause pancreatic lesions is attributable to the cytolytic properties of sodium taurocholate and other bile salts. Diverting bile into the pancreatic duct is not only capable of producing glandular necrosis, but, as was demonstrated by Archibald (1929) and others, it is capable of producing intense edema of the gland, which may or may not be the initial stage of a more extensive and fulminant process. Archibald, confirming the earlier work of Nordmann (1913), showed that injection of infected bile produces acute pancreatic necrosis much more consistently than does injection of sterile bile.

Polya (1912) and others found that injection of active trypsin into the pancreatic duct precipitated acute pancreatitis in practically every experimental attempt. The conclusions drawn were obviously those relating acute pancreatic necrosis to the proteolytic action of trypsin. Criticism of this point of view has been expressed by Mann and Giordano (1923), Sailer and Speese (1908) and McCaughan (1934), all of whom expressed the belief that moderate amounts of any highly irritating fluid injected into the duct under pressure would distend, traumatize and rupture the ductal-acinar system, favoring the development of acute pancreatitis.

The exact relation of the pancreatic enzymes to the necrosis, hemorrhage and destruction of the gland incident to acute pancreatitis is at present a problem. Wangensteen and his colleagues (1931), Rich and Duff (1936) and Brocq and Morel (1919) observed clinically and experimentally that acute pancreatitis usually develops at the height of digestion, and they suggested that increased intraductal pressure associated with acinar rupture probably liberates and activates trypsin, which, in turn, is the essential factor in producing pancreatic necrosis. Dragstedt (1934) and his associates, in a group of ingenious experiments, showed that this particular belief is untenable. Dragstedt



expressed the opinion that the destruction of the pancreas is primarily the result of the toxic and cytolytic action of the bile salts, aided, to be sure, by trypsin, which removes and digests away the surrounding protective proteins. This was neatly demonstrated in part by a series of window implant experiments, the living pancreas being exposed to the digestant action of duodenal contents in one group of animals and to the action of gallbladder bile in another. Acute pancreatic necrosis regularly developed in the latter group only.

Typical cases of acute pancreatitis with fat necrosis and pancreatic destruction may result from a traumatic injury to the abdomen or from degenerative vascular changes in the pancreas. Pancreatic cysts or neoplasms, by their slow growth and compression of the pancreatic ducts, usually cause atrophy and fibrosis of the secretory acini rather than acute pancreatitis, although this is not always so. Case 6 of the present series clearly demonstrates the production of traumatic pancreatitis. A child 7 years of age was struck by the fender of a passing automobile. Minor external contusions were noted at the time of admission to the hospital, and at operation, three days later, the pancreas was found to be engorged and hemorrhagic, with numerous areas of fat necrosis.

In summarizing the factors of importance which play a role in the production of acute pancreatitis, it becomes necessary at times to consider a combination of several factors, none of which acting individually is capable of producing this disease. Thus, the variable and inconstant results of experimental and clinical bacteriologic studies readily indicate that infection alone is rarely a cardinal factor in the causation of acute pancreatitis but is rather a factor of secondary ingress and activity preying on already injured pancreatic tissue. Anatomic and functional observations in the laboratory and the operating room, although conflicting in certain respects, appear to be in general accord with the evidence favoring the reflux of bile into the pancreatic duct as an important primary etiologic agent. The potent necrosing action of bile, the concomitant frequency of acute pancreatitis with disease of the biliary tract and stones and the digestant enzymatic power of the external secretion of the pancreas substantially endorse the common channel theory and the toxic action of bile in producing the disease.

In those cases in which the role of infection, bile or enzyme activity has been relegated to a place of minor import, other factors of pathogenesis, such as vascular injury, trauma or degenerative neoplastic changes, must be considered as a likely cause of acute pancreatic destruction. Dragstedt (1934), in a critical analysis of the subject, stated that undoubted cases have been reported in which each one of these factors has operated to produce an entirely characteristic picture of the disease. Likewise, it has been possible to reproduce the disease in the experimental animal by practically any method that insures a sudden and

fairly extensive necrosis of the pancreatic parenchyma" It must be concluded, therefore, that the solution to the problem of the cause of acute pancreatitis is not yet available, although it is apparent that not one but a combination and interplay of many factors may be responsible for this perplexing disease

#### PATHOLOGIC PICTURE

The appearance of the pancreas varies most often in accordance with four principal pathologic types of the disease observed either at operation or at necropsy. The aspect of the gland at the time of examination may or may not represent a transient phase in the development of pancreatitis. At present there is considerable uncertainty whether the milder types of this lesion merely represent earlier and less severe degrees of an orderly glandular destruction or whether they are distinct yet related pathologic entities. Quick (1932) called attention to a case in which he found edematous pancreatitis at operation and observed extensive pancreatic necrosis at autopsy two days later. Nevertheless, for the purpose of uniform nomenclature it is well to classify the four types as follows, regardless of the overlapping which probably occurs in most cases

Type 1 Acute pancreatic edema, with or without fat necrosis

Type 2 Acute hemorrhagic pancreatitis, with or without fat necrosis

Type 3 Acute gangrenous or necrotic pancreatitis, with or without fat necrosis

Type 4 Acute suppurative pancreatitis, with or without fat necrosis

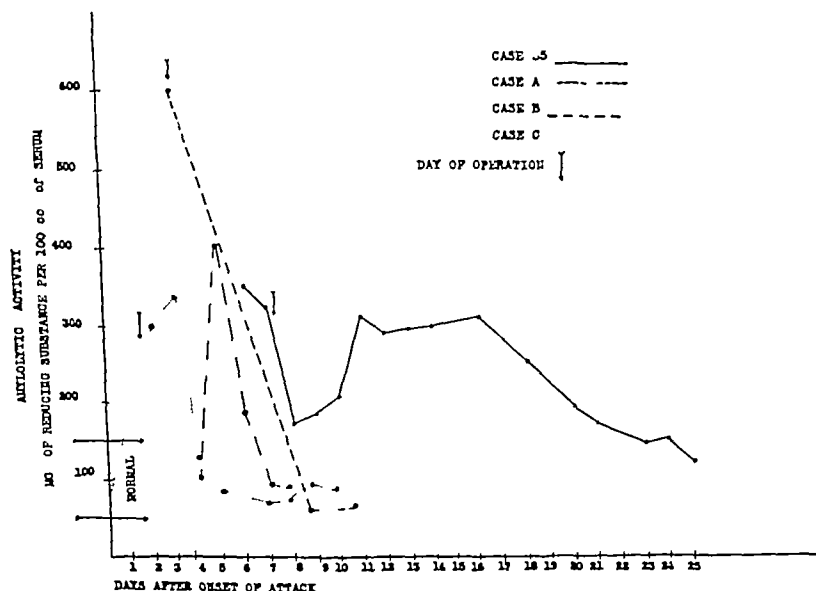
In 2 cases (10 and 12) of the present series the postmortem observations illustrated the essential characteristics of pancreatic hemorrhage and necrosis as observed with types 2 and 3. There were widespread areas of softening and necrosis of pancreatic parenchyma associated with a lesser amount of hemorrhage and surrounded by a small zone of inflammatory reaction. Tissue death *en masse* appeared to be the outstanding feature of acute necrotic pancreatitis, and the transition from the altered to the normal parenchyma in the microscopic and macroscopic specimens was sharp. Hemorrhagic pancreatitis revealed the gland to be dark red and markedly engorged. Microscopically the extravasated blood and fibrin predominated, whereas the degeneration appeared to be secondary, followed by a minimal infiltration of polymorphonuclear cells. Most of the remaining cell nuclei showed pyknosis, others had completely disappeared.

In cases 14 and 35 the pathologic characteristics of acute edematous pancreatitis with fat necrosis were exhibited. The interstitial tissue of the gland was markedly edematous and infiltrated by a small number of

of mononuclear and polymorphonuclear cells. Large accumulations of interacinar edema were observed. There was glossy edema of the surrounding viscera, and no evident pancreatic hemorrhage or necrosis could be demonstrated. The gland was considerably enlarged and distinctly firm to palpation. Twenty cases in the present series, or 57 per cent, revealed bile-stained or blood-stained free peritoneal fluid at operation.

#### CLINICAL MANIFESTATIONS

The value of hospital records in a collected series of cases such as this is only as reliable as the diligence and consideration given the anamnesis and physical examination. Too often the diagnosis of acute



Values for serum amylase in 4 cases of acute pancreatitis. Case 35, described in the text, was a case of type 1 acute edematous pancreatitis with fat necrosis. In cases *A* and *B* the pancreatitis was of types 3 and 4 respectively. More complete amylase studies in these cases were not available. In case *C* a carcinoma of the ampulla of Vater was resected. Autopsy performed on the eighth postoperative day revealed subsiding localized pancreatitis and areas of fat necrosis. Concomitant values for blood sugar were within normal limits in every instance.

pancreatitis is not made because it is not thought of. Such helpful questions as those concerning the exact character and localization of pain and its sharply defined point of radiation are not infrequently neglected, partiality being shown to the more commonplace symptoms of the "run-of-the-mill acute gallbladder." A statistical survey of the reported clinical records of other investigators reveals a familiar lack of uniformity, which, if it can be explained at all, is probably more apparent than real.

*Age Incidence*—Acute pancreatitis may occur at almost any age authentic cases having been reported in which the patients were aged 2 years and 77 years, respectively, but in the present group 60 per cent of the patients were between 30 and 50 years of age. There seemed to be no predilection of mortality for the aged or the young, but death was distributed uniformly through the middle-aged group.

Decade	Cases of Acute Pancreatitis
First	1
Second	0
Third	6
Fourth	9
Fifth	11
Sixth	6
Seventh	2

*Sex Incidence*—Acute pancreatitis appears to be more common among women than among men, which is in accord with its relation to disease of the gallbladder and obesity. Fatalities occurred in direct proportion to the sexual incidence and seemed far more dependent on the pathologic type of the disease than on either the age or the sex of the patient.

	Males	Females
Schmieden and Sebening (1927)	520	950
McWhorter (1932)	32	32
Fallis and Plain (1939)	14	12
Felser (1902)	79	42
Present series	8	27

*Annual Incidence*—The yearly incidence of acute pancreatitis varied irregularly. A larger number of cases was observed during the last seven years than during the preceding twelve, but this was roughly proportional to the increased number of admissions to the hospital. There was no apparent seasonal preponderance, the cases being evenly distributed throughout the year.

Year	Cases	Year	Cases	Year	Cases
1921	4	1927	0	1933	0
1922	3	1928	1	1934	0
1923	0	1929	2	1935	3
1924	3	1930	0	1936	2
1925	1	1931	1	1937	3
1926	1	1932	1	1938	2

First 5 months of 1939

*Gastrointestinal History*—A past history of previous attacks was noted in 71 per cent of the present series. In most these attacks were similar in character and locale to the present illness but mild in severity. Indigestion and rather vague abdominal distress were recurrent in 37 per cent of the cases. Complete freedom from any previous gastrointestinal complaints was found in only 17 per cent. In reference to the subject was omitted in 11 per cent of the cases.

*Pain*—Despite its diverse etiologic and pathologic nature, acute pancreatitis constantly exhibits a sudden onset of rather severe pain. Except for several cases of type 1 pancreatitis, in which the pain was insidious and mild, this was uniformly so in every instance. Persistent epigastric pain was present in 57 per cent, pain in the upper part of the abdomen in 20 per cent, and pain in the right upper quadrant in 20 per cent of the cases. Pain in the left lower quadrant of the abdomen and precordial pain were each recorded on one occasion, although no apparent explanation for this localization was found at the time of operation.

Radiation of pain was noted as present in 74 per cent and absent in 9 per cent of the cases. The numerical incidence of the places to which the pain radiated occurred as follows: back, 21, right shoulder, 3, interscapular region, 3, left shoulder, 1, and umbilicus, 1. No indication of the exact point of radiation in the back was given.

Moynihan (1925) has given a picturesque clinical description of acute pancreatitis. He described the pain of this formidable catastrophe to be by far the worst of all the pains that the human body can suffer. This is undoubtedly true of the hemorrhagic and necrotic types of pancreatic lesions, but with the more benign acute edematous pancreatitis a gnawing, burning pain of lesser intensity is frequently to be encountered.

Vomiting was present in 71 per cent of the cases as recorded in the tabulation. Nausea appeared to be even more constant. The abdominal signs, although persistently found, seemed to be variable in locale and severity. There was no direct relation between the degree of tenderness and the type of pancreatic lesion. Tenderness occurred in the epigastrium in 14 cases, across the upper part of the abdomen in 11 cases and in the right upper abdominal quadrant in 7 cases. Rigidity was present at the time of the entrance examination in 60 per cent of the cases, and the point of maximum muscle spasm was usually the site of maximum tenderness. In general, rigidity was not marked. Jaundice was observed in 43 per cent of the cases. Explanations of its origin are speculative, and the prognostic value of its presence is most uncertain. The cyanosis described by Halsted (1901), a slate gray tinge most noticeable in the upper part of the body, was commented on in only 2 cases. Shock was noted in 3 instances. A definitely palpable mass was felt in 3 cases, although several additional records noted a "suggestive mass" observed by individual examiners. The temperature on admission is indicated in the tabulation of cases. The range of elevation of temperature appeared low and variable and unrelated to the prognosis. The pulse taken at the same time corresponded with the temperature and was in general surprisingly low. As was pointed out by Fallis and Plain (1939), this is at variance with the concept of shock, which

has been thought to be an outstanding symptom of acute pancreatic necrosis. The duration of the attack given in table 2 indicates the length of time from the initial onset of the present illness until the time of operation. In many cases the patient entered the hospital soon after onset of the attack but operation was deferred several days or longer.

TABLE 2—Summary of the Clinical and Laboratory Data in the Present Series of Cases

	Duration of Attack	Vomit ing	Jaundice	Tender ness	Rigid ity	Tem perature, F	Pulse Rate	R B C, Millions per Cu Mm	W B C, per Cu Mm	Type of Pancreatic titis	Resulting Condition of Patient
1	2 days	+	0	RUQ	UA	103.4	146		27,400	3	Improved
2	6 days	+	+	UA	UA	100.4	69		11,100	1	Well
3	6 days	+	0	RUQ	UA	100.2	90		11,600	3	Well
4	4 days	+	0	UA	UA	101.4	134	4.8	12,400	1	Well
5	3 days	+	0	UA	RUQ	99.2	84	4.4	13,500	2	Well
6	3 days	+	0	UA	UA	98.2	100	3.8	21,500	1	Well
7	7 days	+	0	RUQ	0	98.4	92	4.9	10,200	1	Well
8	6 days	+	0	RUQ	RUQ	100.2	104	3.75	11,600	2	Dead
9	2 days	+	0	Epig	Epig	100.0	74	4.25	10,800	1	Well
10	4 days	+	0	UA	0	101.2	100			3	Dead
11	3 days	+	0	Epig	UA	101.6	130			1	Dead
12	4 days	+	0	UA	UA	101.2	116			3	Well
13	14 hours	+	0	UA	UA	99.4	82		11,600	1	Well
14	3 days	+	0	UA	UA	100.0	98		13,100	1	Well
15	10 hours	+	0	UA	UA	101.0	88		14,000	1	Well
16	2 days	+	0	UA	UA	101.0	96	3.7	14,200	3	Improved
17	2 days	+	0	UA	UA	100.6	112	4.56	14,200	3	Improved
18	3 days	+	0	UA	UA	99.2	80	4.5	22,000	1	Well
19	5 days	+	0	UA	UA	103.0	116	4.4	11,000	1	Well
20	10 days	+	0	UA	UA	102.4	100			3	Well
21	5 weeks	+	0	UA	UA	99.4	84			1	Well
22	5 days	+	0	UA	UA	99.4	104			2	Improved
23	3 days	+	0	UA	UA	101.8	104		15,300	3	Improved
24	7 days	+	0	UA	UA	101.6	112		9,300	2	Dead
25	12 hours	+	0	UA	UA	102.0	104	4.03	23,600	1	Well
26	8 days	+	0	UA	UA	99.0	84	6.0	11,900	4	Well
27	3 weeks	+	0	UA	UA	99.8	72	4.19	24,000	4	Improved
28	7 days	+	0	UA	UA	100.8	84	4.66	13,900	1	Well
29	2 weeks	+	0	UA	UA	99.8	88	4.5	12,300	2	Dead
30	6 days	+	0	UA	UA	103.8	113	4.5	31,000	3	Improved
31	5 hours	+	0	UA	UA	99.6	96	4.6	21,400	1	Well
32	2 days	+	0	UA	UA	99.6	88	5.01		1	Well
33	2 days	+	0	UA	UA	101.4	100		16,000	1	Well
34	7 days	+	0	UA	UA	101.0	100	4.0	11,000	1	Well
35	7 days	+	0	UA	UA	99.8	100				

The duration of attack (onset to operation) was difficult to determine accurately in cases in which repeated episodes had occurred during the present illness.

RUQ, right upper abdominal quadrant; LUQ, left upper abdominal quadrant; RLQ, right lower abdominal quadrant; UA, upper part of abdomen; Epig, epigastrium.

#### LABORATORY DATA

**Hematologic Studies**—White blood cell counts revealed a wide range of individual variation, although 65 per cent of the reported counts were found to be below 15,000 per cubic millimeter. In cases in which differential counts were performed there was a marked predominance of polymorphonuclear cells. The red blood cell count offered but scant new or diagnostically significant information regarding the patient's status. Mild anemia of the normocytic class was present in most cases.

and this was in no way severe, even in the presence of the acute hemorrhagic type of pancreatitis with considerable sanguinous peritoneal exudate

*Urinalysis*—Examination of the urine showed albuminuria in a large proportion of the cases. Glycosuria was relatively uncommon. Casts and leukocytes were found occasionally but had little significance.

Chemical studies of the blood were carried out sporadically, and consequently were of little value. Determinations of the amylase content of the blood, urine and feces were deficient in all cases except case 35, as the earlier methods and technic used were chemically questionable, and the results, expressed in unfamiliar units, were rather confusing.

#### DIAGNOSIS

The diagnostic indications of acute pancreatitis fall into three main groups. In the first are the clinical signs and symptoms, in the second are changes in the external pancreatic secretion, and in the third are changes in the internal pancreatic secretion. Results of roentgen examination in the diagnosis of pancreatic disease have thus far been barren. A survey of the literature clearly indicates that the diagnosis of acute pancreatitis is correctly made more often at operation or at necropsy than at the bedside. As has been mentioned, the diagnosis of acute pancreatitis was correctly made in only 11 per cent of the cases of this series. It was suggested as an alternative diagnosis in an additional 17 per cent. The preoperative impression in 70 per cent of the cases was that of acute disease of the gallbladder. Perforated peptic ulcer and acute appendicitis were considered as alternative diagnoses in 14 per cent and 10 per cent respectively.

Many ingenious tests of pancreatic function have been devised, each having its adherents and each its critics who question its utility. The eponymic tests of Cammidge and Loewi have been called esoteric by Coope (1927), who designated them as reactions of dubious foundation. Attempts to determine pancreatic function by examination of the feces and duodenal contents for enzymes have met with little success as practical diagnostic aids in cases of acute pancreatic disease. However, since Magendie (1846) first demonstrated the presence of amylase in blood serum there have been a considerable number of experimental and clinical data to recommend this test as a useful diagnostic adjuvant in cases of this condition. The work of Elman (1931 and 1937) and many others in America and abroad has shown a close correlation between the level of serum amylase and the coincident acute pathologic process in the pancreas. The conflicting results obtained by earlier investigators were probably due to a difference in the methods of amylase determination and must not impugn the reliability of recent, more

uniform reports. Somogyi (1938) has pointed out the inherent vulnerability of older methods, and he has suggested a standard set of conditions and a rapid and practical procedure which, in principle, is entirely in accord with the kinetics of enzyme chemistry.

Several hundred routine serum amylase determinations with a modified Somogyi technique but similar standards have given convincing evidence that the normal level of amylase remains within constant limits in practically all types of disease except acute pancreatitis, in which there is a sudden and significant marked rise. It has been my experience that thyroid and hepatic disease and diabetes may slightly lower the level of serum amylase and that decreased function of the kidney may cause failure of normal excretion of amylase, resulting in slight elevation of the value, but in no condition in which the clinical picture of an "acute abdomen" (other than acute pancreatitis) was present was the level of serum amylase so strikingly elevated. It is true, however, that this value usually reaches its peak within the first forty-eight hours of the disease, and it may precipitously return to normal again within the next forty-eight hours, thus limiting the reliability of the test to the early stages of the attack. Most clinical reports of serum amylase studies agree that in all types of acute pancreatitis there is a significant early rise, regardless of the severity of the lesion. My series of simultaneous determinations of urinary amylase frequently showed a higher value fluctuating within a wider range of individual variation, but generally corroborated the serum amylase level. As yet I have had only a limited experience with the diagnostic value of the serum lipase test, but the enthusiastic reports of Comfort (1937) and of Cherry and Crandall (1932) are an incentive to investigate more extensively and to further its clinical application. Regardless of technical differences both the serum lipase and the serum amylase tests offer valuable information in the diagnostic difficulty of acute pancreatitis, and, when properly evaluated with the clinical signs and symptoms, may reap the benefit of greater diagnostic accuracy and recognition. The fact that practically all observers who have had experience with the serum amylase test find it of genuine value indicates that its usefulness could be expanded, particularly if a conservative therapeutic attitude is to be taken. Peritoneal tap was not performed in this series of cases, but it is recommended by some clinicians as a desirable part of the diagnostic armamentarium.

#### TREATMENT

It was adequately demonstrated by Whipple and Goodpasture (1913) and by Cooke and Whipple (1918) that extensive surgical procedure on animals with experimentally produced acute pancreatic necrosis are contraindicated. The products of pancreatic destruction and peritoneal



exudate are essentially innocuous, and attempts at surgical detergence were of no distinct benefit to the animals. It was concluded from this that the power of pancreatic recuperation is greatest when the gland is left undisturbed in a closed abdomen. The general reaction and toxemia which may occur result from primary nonspecific cellular destruction of the pancreas and cannot be alleviated by operation.

Despite fifty years of surgical therapy, the high mortality of acute pancreatic necrosis remains disconcertingly unaltered. The operations resorted to have shown great diversity. Some surgeons favor immediate laparotomy, while others elect to defer operation. There is apparently no optimum interval for pancreatic appeasement, and thus operation is performed mainly in keeping with the custom of the individual surgeon. If the patient's condition justifies operation, there is considerable variation in the method or combination of methods. The pancreas is drained most commonly by splitting the overlying peritoneum or by dissecting the parenchyma of the gland and removing the necrotic tissue. Anatomically it is hoped that by incising the peritoneal covering of the pancreas its secretory tension will be relieved. However, each individual pancreatic lobule is enclosed by a separate capsule of connective tissue, and in order to insure relief of tension it would be necessary to divide the sheath of each lobule separately. The extensive nature of such a procedure is likely to cause more harm than good. Biliary decompression is accomplished by any one of several operations involving the gallbladder and common duct. The general lack of uniformity in the types of surgical procedures performed has been pointed out by Cole (1938), who suggested that "the value of operation might be overemphasized, although it is undoubtedly true that different procedures would be indicated in different cases."

Until recently there was unanimity of opinion advocating the surgical therapy of acute pancreatitis. Within the last few years, however, the critical reviews of several investigators have repudiated this concurrent belief and favored conservative treatment followed by interval operation if necessary. Nordmann (1938), a surgeon who has devoted a lifelong interest to the study of acute pancreatitis, found, in a careful and objective analysis of the subject, that when the diagnosis of acute pancreatitis can be safely made the omission of any surgical procedure is mandatory. His own case mortality fell from above 50 per cent to 24 per cent under a conservative regimen. Those of his colleagues who resorted to this surgical nihilism found a similar response. Walzel, Bernhard and Haberer found their respective mortality statistics more than halved by following this conservative course of therapy. Mikkelsen (1934) has fostered a Danish school of thought favoring expectant treatment in the care of this disease. He reported a 75 per cent mortality in a

personal series of 39 cases in which the patients were treated non surgically, followed in several weeks by interval operation when indicated. Fifty per cent of his patients were acutely ill at the time of admission to the hospital. After immediate operation his mortality statistics were considerably higher. Walzel (1934) performed surgical exploration in 30 "emergency cases" between 1926 and 1928, with a resultant mortality of 87 per cent. Between 1928 and 1934 he treated 16 patients conservatively, performing an interval operation only when this was indicated by associated disease of the biliary tract, or a deferred operation for well localized suppurative pancreatitis, with a resultant low mortality of 28 per cent.

It is apparent from the literature that there is no agreement as to the comparative value of operative versus the conservative treatment of acute pancreatitis. Because of the infrequent occurrence of this disease the individual surgeon has little opportunity to draw conclusions from his own personal therapeutic experience, he must rely on the empiric dicta of distinguished surgeons who have decidedly influenced the vacillating regimen of treatment. Such prominent authorities as McWhorter (1932), Finney (1933), Korte (1912), Abell (1938), Elhason and North (1930), Wolter (1926) and others have advocated early operation, whereas others equally authoritative—Lewis (1936), Wangensteen (1932), Nordmann (1938) and Walzel (1934)—have recommended conservative treatment or interval operation.

In the present series 4 patients were treated as "surgical emergencies" during the first twenty-four hours of the disease, with a 50 per cent mortality. The 2 patients who died had acute pancreatitis of types 2 and 3, the 2 who recovered had types 1 and 3. Thirty-one patients were operated on during the first week of illness, with a 20 per cent mortality. Of the latter group almost 50 per cent had type 1—acute edematous pancreatitis. The 4 patients treated surgically after the first week of the disease fared still better, all recovered. The average mortality for all types of the disease was 17 per cent, which is rather a decided diminution from the reported operative death rate of other investigators. A more careful study of the deaths from the different types of pancreatitis (table 3) indicates that the mortality rate is directly dependent on the pathologic involvement of the gland and the type of acute pancreatitis. The fact that 54 per cent of the patients in the present series had the mild and less severe phase of the disease is at least a likely explanation of this estimable low mortality figure. The short span of postoperative life has been commented on by many other investigators, and the question has been raised as to the patient's ability to withstand immediate operation. Death within the first 10 postoperative days was noted in 66 per cent of the fatalities in the

series Failure to rally or respond to postoperative therapy was mentioned in the case histories and would appear to corroborate the belief that the added insult of emergency operation was more than the patient's condition warranted

Table 5 indicates the operative procedures followed in the present series of cases Incision and drainage of the pancreas in combination

TABLE 3—Incidence and Mortality Rate of the Four Types of Acute Pancreatitis

	Type 1 (Acute Edematous Pancreatitis)		Type 2 (Acute Hemorrhagic Pancreatitis)		Type 3 (Acute Necrotic Pancreatitis)		Type 4 (Acute Suppurative Pancreatitis)	
	Incl dence, per Cent	Mor tality, per Cent	Incl dence, per Cent	Mor tality, per Cent	Incl dence, per Cent	Mor tality, per Cent	Incl dence, per Cent	Mor tality, per Cent
McWhorter (1932), 64 cases	28	23	42	70	11	70	19	50
Schmieden and Sebening (1927) 1 278 cases*	45	34	25	64	22	66	8	60
Abell (1938) 30 cases	30	0	33	50	30	44	7	0
Present series (1939), 35 cases	54	5	14	60	26	22	6	0

\* The cases of Schmieden and Sebening have been grouped into this pathologic classification

TABLE 4—Statistics on the Reported Personal Series of Cases of Acute Pancreatitis

Observer	Number of Cases	Mor tality per Cent	Comment
1 Quick (1932)	21	38	Early operation cholecystectomy and choledochostomy were the procedures of choice
2. Abell (1938)	30	30	Early operation favored cholecystostomy and peritoneal drainage (Penrose) were the procedures of choice
3 Walzel (1928-1928)	30	87	Early operation in all cases
4 Walzel (1928-1934)	46	28	Conservative treatment or delayed operation
5 Schmieden and Sebening (1927)	38		Cholecystectomy and choledochostomy were the procedures of choice
6 Mikkelsen (1934)	39	7.5	Conservative treatment delayed operation only when indicated
7 Present series (H E Isaacs)	20	15	Cholecystectomy and incision and drainage of the pancreas were the procedures of choice

with one or more ancillary measures were performed in 77 per cent of the cases In the remaining 23 per cent, in which the pancreas was not disturbed, there were no deaths Despite the obvious variety of operative procedures followed in this series of cases, as well as in the personal cases previously reported by individual surgeons (table 4), the diverse mortality statistics signify that an ideal type of therapy for

this disease is yet to be found. Regardless of the operation, the operator or the lack of operation, the mortality of this condition appears to be primarily a result of the pathologic process in the pancreas, and future therapy will undoubtedly be governed by the progress made toward better understanding and control of the origin of pancreatic necrosis. Fact, established by careful correlation of experimental and clinical data, must replace theory and habit before adequate prophylaxis and treatment prevail. Improved diagnostic aids now favor a concerted effort toward more effective therapy, whether it be conservative measures, modified surgical measures or chemotherapy. The virtue of sulfanilamide or its derivatives as an aid in the treatment of acute pancreatitis is as yet undemonstrated.

TABLE 5—*Operative Procedures Employed in the Present Series of Cases*

Operation	Number of Cases	Mortality, per Cent
1 Cholecystostomy and incision and drainage of the pancreas	5	40
2 Incision and drainage of the pancreas	4	25
3 Cholecystectomy and incision and drainage of the pancreas	12	25
4 Cholecystectomy, appendectomy and incision and drainage of the pancreas	2	50
5 Cholecystectomy	3	0
6 Cholecystectomy and choledochostomy	3	0
7 Cholecystectomy, choledochostomy and incision and drainage of the pancreas	3	0
8 Cholecystostomy, appendectomy and incision and drainage of the pancreas	3	0
9 Cholecystostomy	1	0
10 Laparotomy	1	0

#### SUMMARY AND CONCLUSIONS

Acute pancreatitis is a dangerous disease the rarity of which has been overestimated. Important laboratory diagnostic aids, namely, studies of the serum amylase and lipase, indicate that acute pancreatitis may be milder and more prevalent than has been thought.

A consideration of the factors of pathogenesis demonstrates a significant relation of acute pancreatic necrosis to organic diseases and to functional disturbances of the biliary tract. Etiologic agents which seem incapable of producing this disease when acting individually may play a principal pathogenic role when combined. Four separate pathologic types of pancreatitis have been distinguished, and each must be afforded individual attention regarding diagnosis, prognosis, prophylaxis and treatment.

Thirty-five operative cases of acute pancreatitis are reported, with a mortality of 17 per cent. Of these, 54 per cent were of type 1—acute edematous pancreatitis, a rather benign phase of the disease. Pain and tenderness, most often in the epigastrium or the upper part of the abdomen, were constant clinical findings. Radiation of pain to the back

vomiting and a past history of recurrent attacks similar to the present illness were noted frequently

Incision and drainage of the pancreas combined with one or more ancillary procedures were performed in 77 per cent of the cases in the present series. Beneficent experience in using the serum amylase test as a helpful aid in diagnosis may tend to modify conservatively the future surgical treatment of acute pancreatitis.

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# LYMPH IN EXPERIMENTAL BURNS

GEORGE O WOOD, M D

NASHVILLE, TENN

Many studies have been made on the subject of toxin formation as a result of burns. The fact that such abundant evidence both for and against the formation and absorption of toxin has been collected attests to the difficulty of experimentally proving or disproving its existence.

Most of the recent studies have been directed either toward demonstration of a toxin in the blood of burned animals or toward its demonstration in extract from the burned area itself. Thus Robertson and Boyd<sup>1</sup> reported that they had found a toxin in the whole blood and in the cells of burned animals which was not present in the serum and that alcoholic extracts of burned skin proved toxic on injection into guinea pigs, whereas similar extracts of normal skin produced no toxic symptoms. Their second study was repeated by Underhill and Kapsinow, who found that an alcoholic extract of normal skin was just as toxic as a similar extract of burned skin and concluded that the lethal factor in both cases was the alcohol. Harrison and Blalock noted,<sup>3</sup> contrary to the findings of Robertson and Boyd, that isotransplantation of burned skin had no effect on the recipient animal, that transfusion of blood from burned to normal dogs produced no toxic symptoms, and that debridement of the burned area shortened the survival of burned animals.

Harkins, Wilson and Stewart,<sup>4</sup> working with a protein-free extract of skin, demonstrated a depressor substance in both normal and burned rabbit skin. The depressor activity of the extract of burned skin was often less than that of the extract of normal skin. Wilson, Jeffery,

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From the Department of Surgery, Vanderbilt University

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1 Robertson, B, and Boyd, G L. The Toxemia of Severe Superficial Burn. *J Lab & Clin Med* **9** 1-14, 1923, Toxemia of Severe Superficial Burns in Children, *Am J Dis Child* **25** 163-167 (Feb) 1923

2 Underhill, F P, and Kapsinow, R. The Alleged Toxin of Burned Skin, *J Lab & Clin Med* **16** 823-830, 1931

3 Harrison, W G, and Blalock, A. A Study of the Cause of Death Following Burns, *Ann Surg* **96** 36-39, 1932

4 Harkins, H N, Wilson, W C, and Stewart, C P. Depressor Action of Extracts of Burned Skin, *Proc Soc Exper Biol & Med* **32** 913-914, 1935

Roxburgh and Stewart<sup>5</sup> reported that the edema fluid collected from burned areas in rabbits gradually acquired toxic properties and when collected forty-eight hours after burning was frequently lethal to healthy animals of the same species. This action was independent of bacterial activity and seemed to be dependent on the autolysis of injured tissue.

In 1937, Rosenthal<sup>6</sup> reported the finding of a substance in the blood of burned shoats, pigs, guinea pigs and human beings which caused contraction of the virgin guinea pig uterus. It was at first linked with the red blood cells but was later found in the serum, and its properties were sufficiently distinct from those of histamine to differentiate it from that substance. The scrums of convalescent burned animals were found to have the power of neutralizing the substance, but normal serum also had this action to a less marked extent. Kinard and Martin,<sup>7</sup> in studying the vasodepressor action of assay solutions prepared from the blood of normal and that of burned dogs by the Best and McHenry method, concluded that the vasodepressor activity is not due to histamine and that the increased vasodepression produced by assay solutions of blood from burned dogs is accounted for by the increased blood protein concentration due to loss of fluid. They expressed the opinion that the vasodepressor action of the solutions may be due to a protein split product formed from the blood protein during preparation of the assay solution.

The subject of the absorption of substances from burned areas is also somewhat controversial. Thus Underhill, Kapsinow and Fisk<sup>8</sup> reported that after a short latent period the absorption of phenolsulfonphthalein and strychnine from burned areas was much slower than under normal conditions and that substances such as trypan blue, when injected intravenously, readily passed from the blood stream into the burned area but were not reabsorbed to any significant extent. They suggested that the fluid shift in burns resulting from increased capillary permeability is in one direction only, from the capillaries to the tissues. Mason, Paxton and Shoemaker<sup>9</sup> used this same experimental technic

5 Wilson, W. C., Jeffrey, J. S., Roxburgh, A. N., and Stewart, C. P. Toxin Formation in Burned Tissues, *Brit J Surg* **24** 601-611, 1937.

6 Rosenthal, S. R. The Toxin of Burns, *Ann Surg* **106** 111-117, 1937.  
Neutralization of Histamine and Burn Toxin, *ibid* **106** 257-265, 1937.

7 Kinard, F. W., and Martin, F. N. Vasodepressor Activity of Blood of Normal and Burned Dogs. Criticism of Method, *Am J M Sc* **194** 560-562, 1937.

8 Underhill, F. P., Kapsinow, R., and Fisk, M. E. Studies in the Mechanism of Water Exchange in the Animal Organism. II. Changes in Capillary Permeability Induced by a Superficial Burn, *Am J Physiol* **95** 315-324, 1930.

9 Mason, E. C., Paxton, P., and Shoemaker, H. H. A Comparison of the Rate of Absorption from Normal and Burned Tissues. *Ann Int Med* **9** 850-853, 1936.

with sodium iodide and reported that excretion of this substance in the urine was almost identical in the control and in the burned animals

Moon,<sup>10</sup> in discussing traumatic toxemia as a cause of shock, stated

Efforts have been made by the transfusion of blood and otherwise to demonstrate poisonous substances in the blood of animals in shock. The uniformly negative results of such experiments have been emphasized by some as invalidating the conception of traumatic toxemia. Surgeons have made this objection more vigorously than physiologists, perhaps because the latter remember that protein and colloidal substances are not absorbed from tissue spaces into the blood stream but via the lymphatics.

Field and Drinker<sup>11</sup> found that the capillaries are not concerned with absorption of protein from the subcutaneous tissues under normal circumstances but that after plasmapheresis, with substantial reduction of total blood protein, foreign protein placed in the subcutaneous tissues can be detected serologically in the blood when entrance by lymphatic routes has been blocked.

The present study consists primarily of a biologic assay for depressor substances in unmodified lymph obtained from the thoracic duct at varying intervals after receipt of a burn. In several instances, also, dyes were injected into the burned areas, and the lymph of the thoracic duct was observed for evidence of lymphatic absorption of the dye.

#### METHOD

Large animals were anesthetized with ether, and burns were produced by application of red hot soldering irons to the posterior extremities and the lower part of the abdomen. Each hind quarter was burned for approximately five minutes, the resultant burned area comprising approximately one fifth to one seventh of the whole surface. This had been found to be approximately the maximal thermal injury consistent with survival through the period of experimentation. After this procedure the animals were allowed to live normally until ten or twelve hours prior to the lymph studies, when all food and water were withdrawn, to minimize the amount of lymph entering the thoracic duct from the gastrointestinal tract. The animals were then anesthetized with intraperitoneal pentobarbital sodium (25 to 30 mg per kilogram of body weight) and the thoracic duct was cannulated, the external jugular vein being utilized as a conduit. All visible tributary veins and lymphatics from the neck, upper extremities and wall of the chest were ligated. The collection of lymph was facilitated by moderate negative pressure, usually 20 to 30 cm of water. Anesthesia was maintained by intraperitoneal pentobarbital sodium during the period of collection of lymph, and the animals were killed at the end of this period. In several instances Evans' blue azo dye (5 cc per extremity) was injected

10 Moon, V. H. *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938, p. 151.

11 Field, M. E., and Drinker, C. K. *Conditions Governing the Removal of Protein Deposited in the Subcutaneous Tissues of the Dog*, *Am J Physiol* 98: 66-69, 1931.

without pressure beneath the eschar on the medial and lateral aspect of the thigh two to three hours before termination of the experiment, and the lymph was carefully observed for evidence of its absorption.

The unmodified lymph was tested for vasodepressor activity by the method described by Grossman and Williams<sup>12</sup>. This consists of cannulating the abdominal aorta of an albino rat anesthetized with pentobarbital sodium (4 to 5 mg per hundred grams of body weight) and connecting this cannula by means of a three-way stopcock to a small bore mercury manometer for direct reading of the aortic blood pressure or to a syringe for injection of lymph. A small quantity of heparin was introduced as an anticoagulant, and control pressures were obtained. The amount of lymph injected was arbitrarily set at 0.5 cc per hundred grams of body weight, and this was injected over a period of forty-five seconds. Blood pressure readings were obtained at fifteen second intervals for approximately three minutes,

### *Studies of Lymph in Experimental Burns*

Experiment	Interval Between Receipt of Burn and Beginning of Lymph Collection		Period of Lymph Collection		Amount of Lymph Collected Cc	Approximate Change in B. P. Induced in Rat by 0.5 Cc / 100 Gm	Appearance of Dye in Lymph
	Hr	Min	Hr	Min			
1			5	15	44	0	Not injected
2	2	10	1	20	18	0	Not injected
3	12		7	50	45	0	Did not appear
4	17	40	6	50	153	0	Did not appear
5	24		11	30	100	0	Not injected
6	42	30	6		91	0	Not injected
7	47	20	7		122	0	Did not appear
8	60	45	7		13	0	Did not appear
9	66	45	2		21	0	? Faint trace after 45 min
10	90	30	2	30	7.5	0	? Faint trace after 2 hr
11	71	15	1		104	0	? Faint trace after 30 min.
12	71	10	2		80	0	Did not appear
13	114		7		36	0	Did not appear
14	141		7		8	0	Did not appear
15	165		8		5	0	Did not appear

\* Change in blood pressure is recorded as zero if it did not exceed  $\pm 8$  mm. of mercury

at thirty second intervals for approximately six minutes and at one minute intervals for approximately fifteen minutes.

Similar studies were made on 3 normal animals to serve as controls.

### RESULTS

No vasodepressor activity could be demonstrated in the lymph from normal animals. A total of 15 experiments were performed on burned animals at intervals up to one hundred and sixty-five hours from the time of receipt of the burn. In none of these experiments could a vasodepressor substance be demonstrated in the lymph of the thoracic duct when this substance was tested by intra-arterial injection into the albino rat. In a few instances there was a slight transient rise in the arterial

<sup>12</sup> Grossman, E. B., and Williams, J. R., Jr. Relation of Age to Renal Presor Substance, Arch. Int. Med. 62: 799-804 (Nov.) 1938.

pressures following the injection, but this never exceeded 8 mm of mercury and so was interpreted as a volume effect

The natural opalescent character of lymph made positive identification of minute quantities of the blue dye difficult and the results not conclusive. One would, however, get the impression that Evans' blue dye is poorly absorbed by the lymphatics draining burned areas.

In several instances in which the regional nodes were examined no dye could be demonstrated, and the distribution of the dye appeared to be limited to the areas into which it had been injected.

The results of these experiments are presented in the accompanying table.

#### COMMENT

The fact that no vasodepressor substances could be demonstrated in lymph from the thoracic duct of burned animals may have three possible explanations: (1) There may be no such substance formed, (2) if such a substance is formed, its lymphatic absorption may be negligible, and (3) because of lymphodilution, the method of assay used in these experiments may not have been sensitive enough to detect minute quantities which may have been present.

This study can offer no evidence either for or against the existence of a toxin in the burned area itself, but demonstration of such a poison is of minor significance when compared to the question of its absorption. In order to exert a detrimental effect on the organism as a whole, the hypothetical toxin must be absorbed either directly into the blood stream or indirectly via the lymphatics. In regard to the latter, there is some evidence (i. e., the absence of any significant lymphatic absorption of dyes) that suggests that lymphatic absorption from burned areas may be considerably impaired. Thus it is possible that the lymph of the thoracic duct, which was tested for depressor substances, contained little or no lymph from the burned area. If this be true, one could hardly expect to demonstrate in it a toxin which could not be absorbed because of impaired lymphatic function.

In any study on lymph collected from the larger lymph vessels there is the constant and unavoidable factor of dilution of lymph. Because of this, any toxin which might be present could conceivably be so dilute that its presence could not be demonstrated by standard assay methods. In the present study this factor was minimized by injecting relatively large quantities of lymph into small animals.

#### SUMMARY

Lymph collected from the thoracic ducts of burned animals has been tested for vasodepressor activity by intra-arterial injection into albino rats. No vasodepressor activity was demonstrated by this method of study.

## DISEASES OF THE ESOPHAGUS

## ESOPHAGOSCOPIC CONSIDERATIONS

LOUIS H. CLERF, M.D.

PHILADELPHIA

The replacement of inferential diagnostic methods by objective procedures has revolutionized methods of diagnosis and treatment of disease. This is particularly true of diseases of the esophagus. Inspection of the entire length of the esophagus has conclusively demonstrated that many of the inferential diagnoses made in preesophagoscopy were based largely on error.

To understand more fully the symptoms, diagnosis and treatment of esophageal disease it is important to recall that the esophagus is a long, redundant and movable tube contained in great part in the thoracic cavity, where it occupies whatever space may be allotted it by surrounding viscera. Its fixed points are at the hypopharynx and at the diaphragm. Its course is moderately tortuous, and its lumen presents certain anatomic constrictions, several of which are of clinical importance. The upper end of the esophagus is maintained in a state of tonic closure by the cricopharyngeus muscle, the horizontal portion of the inferior constrictor of the pharynx, and opens only with the passage of fluids or food. At the level of the diaphragm, where the esophagus passes from the thorax into the abdominal cavity, there is a constriction, the hiatus esophageus, which is also referred to as the "diaphragmatic pinchcock." This opens only to allow food or fluids to pass and plays an important part in preventing gastric contents from entering the esophagus. Normally the arch of the aorta and the left main bronchus do not encroach on the esophageal lumen to a degree sufficient to produce interference with function.

The esophagus is an integral part of the alimentary canal, and its function is to transfer foods, fluids and oral secretions from the mouth into the stomach. This is accomplished by a coordinated involuntary action of its musculature and is normally unassociated with subjective sensations. In addition to the normal function of swallowing, the esophagus may empty itself of material contained within its lumen by regurgitation. This must be distinguished from vomiting, since in the

case of regurgitation the expelled materials have not reached the stomach and should therefore contain none of the gastric juices or products of gastric digestion

#### SYMPTOMS OF ESOPHAGEAL DISEASE

*Dysphagia*—In the presence of disease of the esophagus the act of swallowing usually gives rise to certain subjective sensations which may be indefinite and undescribable or may be sufficiently marked to interfere seriously with esophageal function. This difficulty in swallowing is designated dysphagia and constitutes the most constant and the most important symptom of esophageal disease. Other complaints often considered as a part of the so-called symptom complex of esophageal disease are odynophagia, regurgitation, loss of weight, hematemesis, pain and hoarseness.

Dysphagia, the most important symptom, may vary from a feeling as of a suggestive lump or other curious sensation in the throat to serious interference with the passage of food. No difficulty is encountered in the recognition of dysphagia in a patient whose esophagus is almost completely obstructed and who is no longer able to swallow solid or soft foods and has lost considerable weight. The greatest difficulties lie in the proper interpretation of vague sensations referable to the esophagus and usually associated with the swallowing of food or of saliva. Often the patient can give no clear account of his symptoms, and unless one is sympathetic to these early manifestations of esophageal disease, errors in diagnosis may result. It is important not to ascribe these subjective sensations to a supposedly functional disorder. Cancer of the esophagus often begins with very slight disturbance of the swallowing function. Recognition of this fact probably would result in earlier diagnosis of an otherwise hopeless disease.

*Odynophagia*—Odynophagia, or painful swallowing, is not commonly observed as an early symptom of esophageal disease. In certain conditions it is never observed. It is usually indicative of extension of inflammatory or neoplastic infiltration to contiguous structures or viscera. In the cervical portion of the esophagus pain is commonly referred to the level of involvement, in the thoracic portion, however, it is usually referred to the substernal region or may extend to the back. Pain referred to the back is a very important diagnostic sign in cases of suspected foreign bodies in the thoracic portion of the esophagus and in cases of esophageal ulceration. It is frequently without value, however, as a means of localization of disease of the thoracic portion of the esophagus, since the pain areas do not correspond to the location of the lesion.

*Regurgitation*—Regurgitation, often confused with vomiting, consists of the ejection of material contained in the esophagus and is due to a reversal of peristaltic action. It is frequently observed in cases of



so called cardiospasm as well as in all conditions associated with a high degree of esophageal stenosis and represents an attempt on the part of an intolerant esophagus to rid itself of contained foods or secretions which cannot be promptly transported to the stomach. In a study of the ejected material one must recall that it has not been in the stomach and therefore lacks digestive agents and products of digestion.

*Loss of Weight*—In cases of disease of the esophagus, loss of weight is primarily the result of progressive starvation and is a late manifestation.

*Hematemesis*—The vomited blood may have been swallowed from the upper air or food passages, or it may have had its origin in the duodenum or in the stomach. Much confusion has resulted from attempting to explain the presence of blood on the basis of inferential methods.

*Other Symptoms*—Hoarseness, dyspnea and cough are not uncommonly observed with certain diseases of the esophagus. Hoarseness may result either from neoplastic infiltration of the larynx itself or from involvement of a recurrent laryngeal nerve. It is a common symptom of cancer of the cervical part of the esophagus. Dyspnea occurs if there is marked narrowing of the airway either by direct infiltration of the tracheal walls or by compression of its lumen, as in the case of a large pulsion diverticulum of the pharynx. Cough results from overflow of secretions into the larynx and may be observed in any of the conditions which interfere with normal esophageal drainage and in which there is laryngeal involvement. Cough also is an important symptom of esophagotracheal or esophagobronchial fistula.

#### METHODS OF DIAGNOSIS

A carefully taken history is of importance. Disturbances in swallowing should be investigated with regard to the mode of onset and duration, the types of food producing them, their localization and the character of the sensations of discomfort produced. Regurgitation should be studied in relation to the taking of food. Unfortunately there often is lacking a clear account of the onset of dysphagia. A patient with extensive cancer may state that he has had difficulty in swallowing for many years or that his difficulty has been only of several weeks' duration. In either case there is a discrepancy between the onset of symptoms and the duration and extent of the disease. This presents insurmountable difficulties which cannot be compensated for by any method of diagnosis or treatment and is one of the reasons why so little progress has been made in the treatment of esophageal cancer.

The mouth, throat, larynx, pyriform sinuses and neck should be routinely examined. Accumulation of fluid in a pyriform sinus is a

positive sign of esophageal obstruction. A general examination of the chest should never be omitted. Serologic studies of the blood should be performed. A positive Wassermann reaction and the signs of aneurysm may readily explain symptoms referable to the esophagus.

With the development of roentgenologic and esophagoscopic methods many of the older diagnostic procedures have become obsolete. Auscultatory methods to determine the function of the esophagus are not trustworthy and should have no place in an esophageal study. The use of the bougie to detect esophageal obstruction is not scientific and is extremely dangerous. It is dependent on meeting with an obstruction and therefore is without value in conditions unassociated with obstruction or in the presence of early lesions that have not become obstructive. While the use of the rigid stomach tube is limited, it is of value in the diagnosis of paralysis of the cricopharyngeal muscle and in carrying out esophageal lavage.

The function of the esophagus can be determined by only one method of examination, namely, fluoroscopic study of the esophagus while the patient is swallowing a radiopaque mixture, i.e., barium sulfate or a bismuth compound. Under certain conditions barium-filled gelatin capsules are of value. No roentgen study of the esophagus should be considered complete until the chest has been studied fluoroscopically and fluoroscopic study of the esophageal function with a radiopaque substance has been made. With the present methods of roentgen study, which permit examination of the patient in various positions, it does not seem possible that the presence of esophageal disease can be overlooked. By these methods any alteration or irregularity in the size of the lumen can be detected, and the presence of strictures, sacculations or deviations from the normal can be ascertained. In most instances the roentgenologist's diagnosis based on a careful study of the esophagus and chest is correct. For absolute certainty it should, however, be supplemented by esophagoscopic data. Certain diseases of the esophagus may be confused with conditions involving the stomach or other portions of the gastrointestinal tract. This is more often observed with lesions involving the lower end of the esophagus. For this reason it is important to consider the esophagus as part of the alimentary tract and to include it in a routine roentgen study.

The esophagoscope provides a method of direct examination. It depends on objective evidence and should therefore be considered the final arbiter in diagnosis of esophageal disease. The interior of the entire esophagus may be minutely inspected, tissue, exudate and secretion may be removed and positive data secured. The esophagoscope is passed by sight. In the hands of one who has been trained in its use the procedure is safe. For this reason no mandrin or other device that would interfere with continuous vision through its lumen is used. As

the examination is done without general anesthesia, it may be repeated at weekly intervals or oftener if deemed necessary. As with most procedures that are noteworthy, special training is necessary to perform esophagoscopy with safety. The esophagoscope is not swallowed by the patient as is the stomach tube. The cricopharyngeus muscle is the stumbling block, and attempts by the inexperienced to pass the esophagoscope as they would a bougie will result in a large percentage of fatal perforations of the pharyngeal wall posterior to the cricopharyngeal fold.

Studies carried out in a haphazard manner usually result in the overlooking of certain examinations. A routine procedure should therefore be adhered to. The following diagnostic steps in order of procedure are suggested:

- 1 Complete history
- 2 General physical examination, including the mouth, nose, throat, pharynx, larynx, pyriform sinuses and neck
- 3 Serologic studies
- 4 Fluoroscopic study of the chest
- 5 Fluoroscopic study of the esophagus with an opaque mixture or a barium-filled capsule, taking of roentgenograms with the opaque mixture or the capsule or both
- 6 Esophagoscopy examination, with a biopsy when indicated

#### THERAPY

For a majority of esophageal diseases, treatment is either mechanical or surgical. In the presence of acute inflammatory conditions or of ulceration the esophagus should be placed at rest as far as possible by liquid diet or by gastrostomy. Of the medicaments, bismuth subnitrate is most commonly employed. It is given in doses of 5 to 15 grains (0.32 to 0.97 Gm.) dry on the tongue after eating and is swallowed without water. It exerts a protective action and is mildly antiseptic. For relief of pain, ethylaminobenzoate (anesthesin), 1 to 2 grains (0.06 to 0.13 Gm.), may be combined with the bismuth preparation. Alkalis are commonly employed in cases of peptic ulcer. Mild protein silver and silver nitrate are useful as topical applications. Accumulation of food in the esophagus proximal to a point of stenosis or in a diverticulum is relieved by swallowing water after eating in cases of slight retention or by esophageal lavage when the retention amounts to a considerable quantity. Dehydration in patients with esophageal stenosis is of serious consequence and should be combated by hypodermoclysis, proctoclysis and intravenous instillation. In cases of stenosis which cannot be promptly relieved, gastrostomy should be performed.

Congenital anomalies of the esophagus, such as atresia, usually terminate fatally within the first few days of life. Study of the esophagus with a small quantity of barium mixture is conclusive. Congenital webs or congenital stenosis with shortening of the esophagus and a thoracic stomach may go unrecognized for many years. The history is important. Patients with such conditions never have been able to swallow normally. In some cases superficial ulceration at the esophagogastric junction may develop. The symptoms simulate those of gastric ulcer, and the condition is often diagnosed as peptic ulcer of the stomach or of the esophagus. Roentgen study of the esophagus with the patient in the Manges "right lateral prone" position exhibits the characteristic dilatation of the stomach immediately above the diaphragm and stenosis at



Fig 1—Roentgenograms of a boy aged 8 years who had had disturbances with swallowing since infancy. The esophagus was short and dilated, there was marked stenosis at the esophagogastric junction, a portion of the stomach was above the diaphragm, and there was absent the normal constriction of the food passageway at the level of the diaphragm. At esophagoscopy examination there was found ulceration at the esophagogastric junction (W F Manges).

the junction of the esophagus and the stomach (fig 1). The esophagoscopy findings are conclusive.

Certain phases of the treatment are medical and include dietetic care, the employment of alkalis and posture. The stenosis may be dealt with esophagoscopically or by the use of an olive-tipped, fenestrated bougie passed over a previously swallowed thread. Topical applications of silver nitrate solution to the superficial areas of ulceration are helpful.

Deviation of the esophagus is observed in deformity of the vertebral column and is usually unassociated with symptoms. Deviation produced by aneurysm or mediastinal tumor is commonly associated with compression stenosis and is productive of disturbance in swallowing.

In the presence of acute esophagitis the substernal pain, dysphagia and occasional hematemesis may suggest some gastric disorder. There is commonly a history of trauma or of swallowing an irritant or a cauterant. Recent burns or scars about the mouth, throat and pharynx are significant. In the early stages, before healing and contraction of the ulcerated areas occur, the roentgen findings are usually inconclusive. It is important to recall that injury to the stomach may occur simultaneously if a cauterant has been swallowed, and the patient may complain of marked epigastric distress. If there remains a question as to the diagnosis, esophagoscopy examination may be performed. It would seem inadvisable, however, to do this immediately after injury, because of the danger of additional trauma and possible perforation of the esophagus.

Chronic esophagitis is commonly observed in persons with chronic alcoholism, in persons who habitually ingest highly seasoned, hot or irritating foods, in the presence of certain constitutional states and in cases of stenosis with retention of food and presents no problem in diagnosis if esophagoscopy examination is performed.

Benign ulceration of the esophagus, particularly in its lower third, may be confused with gastric disease. There may be dysphagia. Pain is a frequent symptom. It usually is referred subinternally or to the region of the ensiform cartilage and may extend through to the back. Spastic stenosis involving either the cricopharyngeal muscle or the diaphragmatic pinchcock may occur. There is often associated esophagitis. Regurgitation and hematemesis may be observed. In cases of simple peptic ulcer of the esophagus, in those cases of congenital shortening of the esophagus and thoracic stomach in which there is ulceration at the esophagogastric junction and in cases of hiatal hernia, pain behind the lower end of the sternum extending to the back is significant. Odynophagia is common. Patients are conscious of food passing a tender point. Pain commonly begins immediately after eating and is promptly relieved by alkalis. Heartburn is a common symptom. This may be increased on the patient's assuming a prone posture. Dysphagia is usually not observed during the early stages. It may develop if stenosis occurs during healing. These ulcers commonly are superficial, covered with thin, grayish exudate and surrounded by a narrow inflammatory zone. They present no roentgen evidence unless there is secondary stenosis or deformity. The esophagoscopy appearances are characteristic, the diagnosis can be verified by histologic examination of the tissue.

Tuberculous ulceration of the esophagus is always associated with demonstrable tuberculosis elsewhere. If there is doubt, esophagoscopy examination, biopsy and bacteriologic studies will give conclusive findings.

Syphilitic ulceration may be associated with cancer or with secondary esophageal infection. A patient with carcinoma may have a positive Wassermann reaction. Biopsy should always be done. In questionable cases the therapeutic test is of value. Cancer is the most common cause of ulceration of the esophagus in adults. Roentgen study of the swallowing function and esophagoscopy examination followed by biopsy are conclusive diagnostic methods.

Vincent's infection, blastomycosis and the rarer lesions of the esophagus may cause confusion in diagnosis. The diagnosis is usually dependent on bacteriologic and histologic examination of material removed esophagoscopically.

Varicosities at the lower end of the esophagus may be the source of spontaneous hemorrhage. Varix practically never occurs in the upper part of the esophagus. If regurgitated, the blood is bright red and alkaline in reaction. More often, however, it is acid in reaction and of a "coffee ground" character, having been swallowed into the stomach and then vomited. Evidences of obstruction of the portal vein are important. The presence of varices at the lower end of the esophagus can be demonstrated esophagoscopically, but failure to observe them is not conclusive.

Stenosis of the esophagus may result from pressure due to periesophageal disease or from lesions in the esophageal wall itself.

Compression stenosis of the lower part of the esophagus may be produced by aneurysm, cardiac enlargement, enlargement of the left lobe of the liver, malignant disease of any of the intrathoracic viscera or lymphadenopathy. The common symptom is dysphagia. A general physical examination, serologic studies, roentgen study of the chest and functional studies of the esophagus will usually suffice to establish a correct diagnosis. If a question exists, esophagoscopy procedures may be used.

Cicatricial stenosis of the esophagus should not be confused with gastrointestinal disease, as the symptoms are practically always esophageal in origin, consisting of dysphagia, loss of weight (depending on the degree of stenosis) and regurgitation. Temporary lodgment of food producing complete obstruction, chronic esophagitis and occurrence of spasm, particularly if the stricture is at the lower end of the esophagus, may cause confusion in diagnosis. In addition, it must be recalled that patients who have swallowed strong acid solutions may sustain injury to the stomach as far as the pylorus. There may be a history of swallowing a corrosive substance, development of symptoms during one of the prolonged fevers, such as scarlet fever, peptic ulcer of the esophagus, syphilis or trauma following obstruction or prolonged sojourn of a foreign body. Roentgen study and use of the esophagoscope

should leave no doubt as to the diagnosis (fig 2) The esophagoscopic findings of areas of scarring, granulation tissue with esophagitis and dilatation of the esophagus proximal to the point of stenosis are characteristic It is of interest to note that in cases of esophageal stenosis of long standing the stomach is often contracted, probably from lack of distention by food and relative inactivity

The treatment of strictures depends on the degree of narrowing and the extent of involvement Dilation is a slow process and must be carried out over a long period Interference with nutrition is a definite indication for gastrostomy For a gastrostomized patient, the safest and best



Fig 2—Multiple strictures of the esophagus resulting from accidental swallowing of a concentrated solution of lye. There was moderate dilatation of the esophagus proximal to the strictures Gastrostomy became necessary for feeding purposes The strictures were dilated by retrograde bougienage (W F Manges)

method of treatment is retrograde bougienage For patients not requiring gastrostomy, esophagoscopic bougienage or the passing of a fenestrated olive-tipped bougie over a previously swallowed string is the method of choice Bougienage without a guide is hazardous and often results in perforation with fatal mediastinitis

Spasmodic stenosis of the cricopharyngeus muscle is observed in cases of cancer of the lower end of the esophagus, of peptic ulcer and of diseases of the gastrointestinal tract This condition may simulate and is often diagnosed as "globus hystericus" Such a diagnosis is justifiable only after every known diagnostic means has been utilized to rule out disease of the alimentary canal

Cardiospasm, phienospasm or preventriculosis, occasionally associated with disease of the stomach, biliary apparatus or appendix, is frequently mistaken for gastrointestinal disease. The common symptoms are discomfort or a sense of fulness referred to the epigastrium and relieved by regurgitation, inability to swallow certain foods, such as cold liquids, loss of weight (which may be marked) and, occasionally, severe pains about the region of the ensiform cartilage, extending through to the back. The cause is obscure. The occurrence of associated disease of the gastrointestinal tract or of the gallbladder is probably



Fig 3—*A*, roentgenogram in a case of cardiospasm of seven years' duration occurring in a woman aged 32 years. The symptoms were dysphagia with liquids and solid foods, regurgitation of food and loss of weight. The esophagus was greatly dilated and terminated in a smooth, blunt end at the level of the diaphragm. At esophagoscopy there were found retention of food and chronic esophagitis. No difficulty was encountered in passing the esophagoscope through the hiatus esophageus into the stomach, demonstrating that there was an absence of organic stenosis. Prompt improvement followed aerostatic divulsion of the hiatus esophageus (J T Farrell Jr). *B*, roentgenogram showing a traction diverticulum and a dilated esophagus suggesting cardiospasm in a man aged 56 years. Dysphagia, regurgitation and loss of weight were of six months' duration. At esophagoscopy examination there was found an organic stenosis of the esophagus at its lower end, apparently due to an infiltrating neoplasm. Abdominal exploration revealed an extensive carcinoma involving the cardia (M Dillman).

comcidental. Deformity of the liver and endocrine disturbances have been described as etiologic factors. There is a dissociation of the swallowing mechanism which probably is the result or disease of the



esophagus or of its nerve supply. Fibrosis of the esophageal wall has been a common finding. The degree of dilatation of the esophagus is variable. Dilatation is always present, in cases of extreme involvement the esophagus may hold as much as 2 liters. The regurgitated material is sour and stale and lacks all the constituents of gastric juice. Foods eaten twenty-four hours previously often can be identified. Unless the gastroenterologist is aware of this condition he will siphon off the test meal from the esophagus instead of from the stomach, and the analysis, lacking all constituents of gastric contents, will lead to erroneous conclusions. Patients with cardiospasm usually are unable to swallow a diagnostic tube. A roentgen check-up of the position of the tube should therefore precede an attempted gastric analysis in the case of a patient with cardiospasm or any condition associated with dysphagia. The diagnosis of cardiospasm can usually be made by the roentgenologist (fig 3 *A*). The esophagoscope should always be used, however, to corroborate the diagnosis and to rule out cancer of the cardiac end of the stomach with the growth extending to the hiatus esophageus and producing esophageal symptoms simulating cardiospasm (fig 3 *B*). The esophagosopic appearances are characteristic. The thoracic portion of the esophagus is greatly dilated, and a large quantity of fluid and, at times, of residual food is present. The walls are thickened, at times leathery, and are thrown into numerous folds. The mucosa presents a furred or pasty appearance, suggesting a heavily coated tongue. Chronic esophagitis is present, and erosion of the mucosa may be observed. No resistance is encountered in traversing the hiatal orifice, although it often is difficult to find, owing to the numerous folds and the enormous dilatation. Antispasmodics are of value in occasional cases, although the condition is not primarily due to spasm. Regulation of the diet with avoidance of coarse foods, use of bismuth subnitrate dry on the tongue and esophageal lavage, particularly before retiring, are beneficial. None of these procedures, however, is entirely effective. The best results are secured by division of the diaphragmatic pinchcock by hydrostatic or mechanical dilation. Relapses are not uncommon.

Diverticula of the esophagus are divided into pulsion and traction forms. The pulsion form is anatomically a diverticulum of the lower end of the pharynx (fig 4, *A* and *B*). The neck or orifice of the pouch is at the level of the cricopharyngeus muscle, while the fundus extends downward behind the esophagus. It occurs more often in males than in females and is usually observed after the fiftieth year of life. A point of congenital weakness between the oblique and transverse fibers of the cricopharyngeus muscle is considered of etiologic importance. Cricopharyngeal spasm is unquestionably an added factor. Disturbance in swallowing is the first symptom noted. This may consist only of a gurgling sound when fluids are swallowed. Later there is actual dif-

difficulty in swallowing foods. As the pouch increases in size, it may exert sufficient pressure against the subdiverticular portion of the esophagus to produce marked dysphagia and seriously impair nutrition. Retention of food in the pouch results in gravitation of the food into the pharynx when the patient assumes a prone posture. This necessitates

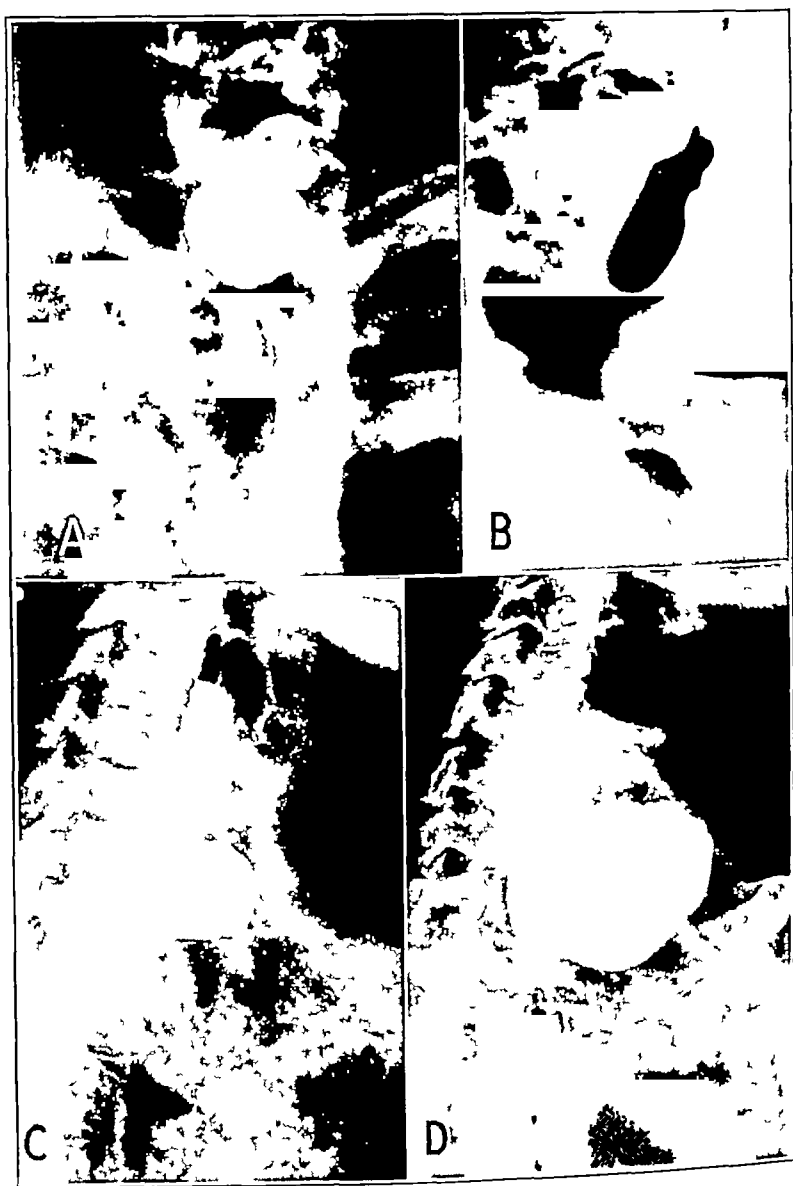


Fig 4—*A* and *B*, roentgenograms of a pulsion diverticulum of the pharynx. In the lateral view, the partially filled pouch displaced the esophagus forward and narrowed the barium column, producing compression stenosis. The pouch was extirpated and the pharyngeal wall repaired by a one stage combined diverticulectomy (W F Manges). *C* and *D*, roentgenograms showing how the pouch in cases of pulsion diverticulum of the pharynx tends to increase progressively in size. Comparison of *C*, made in 1930, and *D*, made in 1934, showed a striking increase in the size of the pouch. There was marked dysphagia (J T Farrell).

frequent clearing of the throat and may cause choking sensations. The breath has a stale, sour odor. In cases of long-standing involvement, respiratory symptoms may result from aspiration of food particles and secretions, particularly while the patient is sleeping. Roentgen ray examination with a barium mixture gives practically conclusive results, and with esophagoscopy the diagnosis becomes exact (fig 4, *A* and *B*). Bougienage is inconclusive, unsafe and unnecessary. No organic stenosis of the esophagus is present. Dysphagia results from compression of the esophagus by the distended pouch. A diet of liquids and soft foods, lavage of the pouch immediately after eating and the use of bismuth subnitrate will allay the chronic inflammatory changes and prevent the distress caused by retained foods. Surgical extirpation of the pouch is the treatment of choice and should be done unless there is a contraindication. The pouch invariably becomes larger with increasing dysphagia, nutritional disturbances and respiratory symptoms from overflow of secretions (fig 4, *C* and *D*).

The traction form of diverticulum occurs in the lower portion of the thoracic end of the esophagus and rarely causes symptoms. It is usually discovered accidentally by the roentgenologist in a routine gastrointestinal study. Traction diverticulum results from adhesions between the esophagus and surrounding structures, such as enlarged mediastinal lymph nodes or thickened pleura (fig 3 *B*). Treatment is rarely required. In the presence of the occasional pouch with retention, posture may be advantageously employed.

Hiatal hernia, or herniation of a portion of stomach through the esophageal opening in the diaphragm into the thoracic cavity, may give rise to esophageal symptoms. There may be dysphagia, distress and even pain on swallowing foods, substernal pain, which often passes through to the back, and occasionally esophageal obstruction with regurgitation.

Results of studies made with the patient in the Manges or the Trendelenburg position are commonly characteristic (fig 5). At esophagoscopy examination one finds gastric mucosa well above the level of the diaphragm, there is an absence of the normal hiatus or pinch-cock appearance of the esophagogastric junction, and superficial ulceration may be observed at this point.

The treatment commonly is surgical.

Cancer of the upper end of the esophagus should not be confused with gastric disease. Difficulty in the localization of symptoms should always suggest that the entire esophagus must be considered when one is investigating esophageal or epigastric symptoms. The diagnosis of cancer commonly is made late, in spite of the fact that by careful roentgen study of the esophagus and by esophagoscopy examination one can recognize abnormalities that produce very moderate narrowing

of the esophageal lumen. Regurgitation, loss of weight, hematemesis and pain occur late in the disease and commonly represent a high degree of stenosis with periesophageal extension. Patients often will not consult a physician until the disease is advanced. Recognition of vague sensations on taking food, cricopharyngeal spasm or a feeling that food temporarily lodges in the esophagus in swallowing are symptoms of esophageal cancer, and prompt investigation of these by roentgen study and use of the esophagoscope, with biopsy, may aid in diagnosis early in the disease. Interpretation of these symptoms as evidences of a neurosis is inexcusable. The use of blind bougienage is unscientific and



Fig 5—Hiatal hernia of the stomach occurring in a woman aged 65 years. Dysphagia, "heartburn," and associated epigastric pain were of five years' duration. At esophagoscopic examination there was no stenosis of any part of the food passageway, and the normal hiatal constriction was absent. Superficial ulceration was present at the esophagogastric junction (K. Kornblum).

dangerous. Cancer involving the cardiac end of the stomach may first manifest itself by hiatal spasm, there may be extension upward, producing infiltrative stenosis (fig 3 B). Roentgen evidence of hesitation of a thick barium mixture at the hiatal level is an indication for direct inspection of the esophagus and stomach. The roentgen appearances of cancer are commonly diagnostic (fig 6). Dilatation of the esophagus proximal to the growth is not so marked as that observed in cases of stenosis due to benign lesions.

Esophagoscopically, cancer of the esophagus is manifested by fungation, ulceration or infiltration. A specimen for biopsy may be safely taken from the areas of ulceration or fungation. In cases of compression stenosis or of submucosal infiltration with a normal overlying mucosa it is inadvisable to secure a specimen of tissue. Biting through a normal mucosa with tissue forceps opens avenues for infection.

Treatment of cancer of the esophagus has been extremely disappointing. Surgical extirpation should offer the greatest hope, but this is largely theoretic, as patients rarely are seen in the early stages of the disease and usually are poor risks for such a formidable procedure.



Fig 6—Irregular stenosis of the esophagus occurring in a man aged 52 years who complained of dysphagia and loss of weight. At esophagoscopic examination there was found an extensive fungating stenotic lesion beginning at the middle third of the esophagus. Biopsy was done. The histologic diagnosis was squamous cell carcinoma (K. Kornblum).

The results today from roentgen ray and radium treatment and from chemotherapy are not encouraging. The measures commonly employed are palliative, to prevent starvation. These consist of intubation of the esophagus, dilation of the cancerous stenosis and gastrostomy.

Foreign bodies in the esophagus should present no difficulties that might lead to confusion with gastrointestinal disease, it is a common experience, however, to see little children with esophageal foreign bodies who have been treated for gastric trouble because of regurgitation which

was erroneously interpreted as "vomiting." A roentgen study of the neck and chest often revealed a foreign body, esophagoscopy removal of which cured the patient of the "gastric trouble." Sharp, pointed or irregular objects lodged in the cervical portion of the esophagus may produce a sticking sensation or actual pain localized at the point of lodgment. In the thoracic portion of the esophagus localization is not so accurate. I observed a man who swallowed a denture which lodged in the esophagus and was localized roentgenologically at the level of the suprasternal notch. The symptoms were dysphagia and pain referred



Fig 7—Roentgenogram made after the patient had swallowed a barium-filled gelatin capsule, revealing lodgment of the capsule in the upper thoracic portion of the esophagus. There was a history of choking while eating fish, followed by a sticking sensation in the region of the suprasternal notch. At esophagoscopy examination a portion of fish bone was removed (W F Manges)

to a point 1 inch (2.5 cm) below the ensiform cartilage, slightly to the left of the midline. After esophagoscopy removal of the denture the pain was promptly relieved. Foreign bodies, particularly food, may lodge in a stenotic esophagus narrowed by cicatricial changes, cancer or periesophageal disease.

In the case of foreign bodies that are opaque to the roentgen ray the diagnosis is obvious. It must be recalled that bones and other

nonmetallic materials, normally somewhat opaque to the roentgen ray, will not show on the film when superimposed on the shadows of the soft tissues and the bony skeleton. In these and in the nonopaque varieties, difficulty in diagnosis may be experienced, however, with the aid of a radiopaque material used in mixture or in capsule with the patient properly placed, the roentgenologist can give valuable data (fig 7). In case of doubt, diagnostic esophagoscopy is clearly indicated. The only method of treatment worthy of consideration is esophagoscopic removal.

"Retrograde esophagoscopy," the transgastric introduction of a retrograde gastroscope through a gastrostomy fistula, performed for purposes of alimentation, has greatly contributed to knowledge of the esophagus in the presence of stenotic or atresic lesions which could not be traversed by peroral esophagoscopic means. The technic is similar to that employed in retrograde gastroscopy. It is of great aid in placing an endless string in those cases of extensive cicatricial stenosis of the esophagus in which a string cannot be got through perorally for retrograde dilation. In these a flexible-tipped filiform bougie passed by retrograde esophagoscopic methods through the strictures can be recovered in the pharynx, a string secured to the bougie and the bougie with the string attached withdrawn through the esophagoscope. It is also indispensable in penetrating the cicatricial barrier by the combined peroral and retrograde method under fluoroscopic guidance in cases of cicatricial atresia of the esophagus.

# CONGENITAL ATRESIA OF THE ESOPHAGUS

## A STUDY OF THIRTY-TWO CASES

THOMAS H LANMAN, MD

Assistant Professor of Surgery, Harvard Medical School, Visiting  
Surgeon, Children's Hospital

BOSTON

Congenital atresia of the esophagus is a rare anomaly. The experience of any one physician with this condition is necessarily limited. The literature on the subject is large, but most of the articles deal with a few individual cases plus a review of previously reported cases. The total number of reported cases is now about 300.

In the past eleven years, 32 cases of congenital atresia of the esophagus have been observed in the surgical service of the Children's Hospital. Thirty patients were submitted to operation, and complete autopsy was performed on the other 2 patients. In the 30 operative cases the surgical findings were supplemented by complete postmortem examination in 22 instances.

Cases observed in this hospital before 1929 are not considered here. Their inclusion would not change significantly the statistical data, and it is only since 1929 that a discussion of the forms of surgical treatment has been of value. Until then gastrostomy was the only surgical procedure used, and it was, of course, uniformly unsuccessful. This report is a critical analysis of 30 operative cases. All are from the surgical service of the Children's Hospital, and the operative procedures were carried out by a small group of closely associated surgeons, 16 of them being done by me.

There are many excellent reviews of reported cases, particularly those of Mackenzie,<sup>1</sup> Plass,<sup>2</sup> Hacker and Lotheissen,<sup>3</sup> Gage and Ochsner<sup>4</sup> and Rosenthal.<sup>5</sup> In many instances these reports include a

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From the Surgical and Pathologic Services of the Children's Hospital and the Departments of Surgery and Pathology of the Harvard Medical School.

1 Mackenzie, M. *Malformations of the Esophagus*, Arch Laryng **1** 301, 1880.

2 Plass, E. D. *Congenital Atresia of the Esophagus with Tracheoesophageal Fistula*, Johns Hopkins Hosp Rep **18** 259, 1919.

3 Hacker, V., and Lotheissen, G. *Chirurgie der Speiseröhre*, in von Bruns, P. *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1926, vol. 34, p. 192.

4 Gage, M., and Ochsner, A. *The Surgical Treatment of Congenital Tracheoesophageal Fistula in the New Born*, Ann Surg **103** 725, 1936.

5 Rosenthal, A. H. *Congenital Atresia of the Esophagus with Tracheoesophageal Fistula. Report of Eight Cases*, Arch Path **12** 756 (Nov) 1931.



discussion of the embryologic factors causing this anomaly Plass<sup>2</sup> and Rosenthal<sup>5</sup> in particular have given excellent descriptions of the embryologic considerations

As this paper is primarily a discussion of the operative procedures, only a brief mention of the embryologic aspects of this anomaly is needed Both the trachea and the esophagus are formed from the single tube of the primitive foregut The lung bud appears as a projection on the anterior wall of the foregut at the region where the bifurcation of the trachea will occur Normally the primitive foregut divides into two tubes, the trachea and bronchial tree anteriorly and the esophagus posteriorly The division of this single tube into two occurs as a result of fusion in the midline of longitudinal projections arising from both lateral walls The incomplete fusion of this septum at the level of the anteriorly growing lung bud results in the various types of anomaly observed Strong and Cummins<sup>6</sup> have given an elaborate classification of all the various types and subdivisions of the anomalies that may occur

Vogt<sup>7</sup> in 1929 published from this hospital an article in which he suggested for the variations of this anomaly a comparatively simple classification which meets all needs as far as clinical application is concerned With type 1 there is a complete absence of the esophagus This is extremely rare With type 2 there is a blind end to both the upper and the lower segment of the esophagus, but there is no communication with the trachea from either segment This is rare With type 3 there are three varieties With type 3a the upper segment communicates with the trachea, the lower segment being blind This is rare With type 3b the upper segment is blind, and the lower segment communicates with the trachea at or about the level of the bifurcation of the trachea This is by far the commonest type With type 3c both the upper and the lower segment have a communication with the trachea This is rare

In this series there were 19 boys and 13 girls Twenty-nine, or 91 per cent, had anomalies of type 3b One anomaly was of type 2, 1 of type 3a and 1 of type 3c I have not seen any instance of type 1 These figures agree closely with those reported by others Mackenzie<sup>1</sup> in 1880 reviewed 62 cases of esophageal atresia in which 40, or 60 per cent, of the patients showed a blind upper segment and a fistula between the lower segment and the trachea (type 3b) Hacker and Lotheissen<sup>8</sup> in 1926 published a series of 223 cases of which 173, or 77 per cent, had the same type of fistula of the lower segment In 1931 Rosenthal<sup>5</sup> reported a series of 255 cases in which 205 patients, or 80 per cent, had

<sup>6</sup> Strong, R. A., and Cummins, H. Congenital Atresia of the Esophagus with Tracheo Esophageal Fistula, *Am J Dis Child* **47** 1299 (June) 1934

<sup>7</sup> Vogt, E. C. Congenital Esophageal Atresia, *Am J Roentgenol* **22** 463, 1929

this type of esophageal atresia with fistula. The more careful examination of such patients probably explains the more common finding of a tracheal fistula associated with the esophageal atresia. The associated tracheoesophageal fistula is the reason for many of the technical difficulties in operative treatment.

#### ASSOCIATED ANOMALIES

Many writers have called attention to the frequent association of other anomalies with tracheoesophageal fistula, particularly anomalies of the gastrointestinal tract. In this series there were 7 instances of associated anomalies of the gastrointestinal tract which if not treated by operation were in themselves incompatible with life. In 5 instances there was an imperforate anus, and there was 1 instance each of atresia of the ileum and atresia of the duodenum. One patient had both

*Distribution of Various Types of Anomaly*

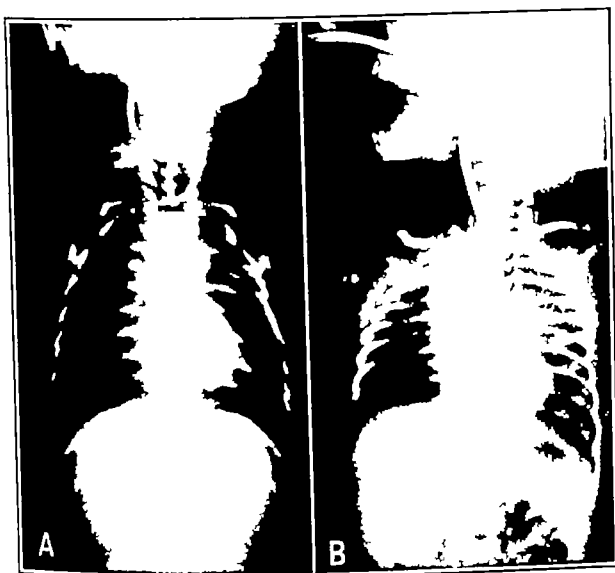
	Cases	Per Cent
Type 1	0	0
Type 2	1	3
Type 3a	1	3
Type 3b	29	91
Type 3c	1	3
	—	—
	32	100

duodenal atresia and an imperforate anus, and another had a rectovesical fistula in addition to the imperforate anus. Other less important anomalies were Meckel's diverticulum, which occurred in 5 cases, various anomalies of the heart and blood vessels, which were found in 7 instances, and anomalies of the genitourinary tract, which were observed in 6 cases. The patients in case 8 and case 11 were children of the same parents.

#### SYMPTOMS AND DIAGNOSIS

The symptoms are characteristic and striking. They are attacks of choking and cyanosis occurring in the first few hours of life, and almost invariably these attacks are aggravated whenever any fluid is offered the infant. Attempts to swallow fluid are followed by immediate regurgitation and are usually accompanied with evidence of aspiration of fluid into the air passages, shown by choking, coughing and cyanosis. Between attacks it is usually noted that the infant has an excessive amount of mucus or saliva coming from the mouth. Often these secretions are described as frothy in appearance and indicate the overflow of secretions into the trachea. The aforementioned symptoms should suggest the diagnosis, and if the presence of an anomaly is suspected

the taking of a roentgenogram without the use of a contrast medium is helpful. Whether or not there is a fistula associated with the atresia, the giving of barium sulfate by mouth is accompanied by great danger and should never be done. Aspiration of barium sulfate alone into the air passages results in an irritative type of pneumonia. Aspiration of iodized poppyseed oil is relatively harmless in itself, but even with the most careful technic there will be some aspiration of the oil plus mucus and saliva containing the oral organisms from the upper segment of the esophagus. It is important also to realize that the use of a contrast medium will not give any helpful diagnostic information that cannot be obtained without its use. Before the plain roentgenogram is taken, a



A, roentgenogram taken without a contrast medium, showing the catheter obstructed in the upper segment of the esophagus. There is no gas in the stomach or bowel. This indicates that the anomaly is either type 2 or type 3a. B, roentgenogram taken without a contrast medium, showing the catheter obstructed in the upper segment of the esophagus and gas in the stomach and bowel. This is the commonest type of anomaly, type 3b. The rare type 3c would give a similar picture.

soft rubber catheter should be passed down the esophagus as far as it will go. The level of the upper pouch can be clearly demonstrated by this procedure. If there is no gas in the stomach or bowel, the anomaly is either type 2 or type 3a. If the catheter meets an obstruction and there is gas in the stomach and bowel, it is either type 3b or type 3c. For practical purposes this is all the differentiation needed preoperatively, as will be shown later (see accompanying illustration).

## REPORT OF CASES

CASE 1—J F, a boy, entered the hospital Sept 5, 1929, at the age of 12 days, with a typical history of attacks of choking, cyanosis and the immediate vomiting of fluids taken by mouth

Roentgen examination with barium sulfate showed a blind upper segment of the esophagus, the lower end communicated with the trachea, as was shown by the gas in the stomach and bowel. The anomaly was of type 3b. There was evidence of bilateral pneumonic infiltration.

An anterior gastrostomy was done Sept. 5, 1929 (Dr C G Minter). The mediastinum was then explored through the back by the extrapleural approach. The lower segment of the esophagus communicated with the trachea just above the bifurcation. The blind upper end was somewhat dilated. The lower segment of the esophagus was separated from the trachea, and the fistula, which was about  $\frac{1}{8}$  inch (0.32 cm) in diameter, was closed. The lower segment of the esophagus was freed, a catheter was inserted, and the opening of the lower part of the esophagus was sutured to the skin just to the right of the spine. The child died at the end of the operation. No autopsy was performed.

CASE 2—M McL., a girl, entered the hospital Dec 29, 1929, at the age of 1 day, with a history of large amounts of mucoid saliva coming from the nose and mouth shortly after birth and also of "choking attacks."

Roentgen examination with barium sulfate showed atresia of the esophagus at the level of the bifurcation of the trachea. There was a considerable amount of opaque material in the main bronchial tree. The stomach and intestines contained a large amount of air, demonstrating a communication between the lower part of the esophagus and trachea. The anomaly was of type 3b. There was diffuse peribronchial congestion but no gross consolidation.

Operation (December 30) consisted of exploration of the mediastinum through the posterior extrapleural approach (Dr W E Ladd). The upper segment of the esophagus was dilated and blind. The lower end of the esophagus joined the trachea just at the bifurcation. The communicating segment was doubly tied and cut between the ties. The lower segment of the esophagus was brought out through the back and sutured to the skin. The patient died just as the operation was completed.

Postmortem examination showed bilateral pneumonia and clearly demonstrated the danger of using barium sulfate in these cases. The bronchial tree in this case, as in the previous one, was filled with aspirated barium sulfate.

CASE 3—J C P, a boy, entered the hospital July 10, 1930, at the age of 4 days, with a typical history of regurgitation of liquids associated with attacks of cyanosis and choking and of an excessive amount of "mucus" coming from the mouth and nose. Coarse rales were heard throughout both lungs, and roentgen examination showed the upper blind pouch of the esophagus at the level of the third dorsal vertebra and gas in the stomach and intestines.

Operation (July 10) consisted in exploration of the mediastinum through the posterior extrapleural approach (T H L). The lower segment of the esophagus communicated with the trachea at its bifurcation. The anomaly was of type 3b. The communicating segment was doubly tied and cut between the ties. The lower segment of the esophagus was freed and sutured to the cutaneous wound. A better exposure was obtained in this case than in the 2 previous ones, but a small hole was made in the pleura. The child lived about twelve hours.

Postmortem examination showed bilateral pneumonia. There were bilateral megaloureters as an associated anomaly.

CASE 4—J P, a boy entered the hospital Aug 17, 1930, at the age of 5 days, because of regurgitation of all fluid taken by mouth and because of bilateral pneumonia. Roentgen studies with barium sulfate had been done at another hospital. After transfusion the child improved slightly, and on August 18 an exploration of the mediastinum was made through the posterior extrapleural approach (Dr G D Cutler). The upper segment of the esophagus ended blindly. The lower segment communicated with the trachea just above its bifurcation. The anomaly was of type 3b. The fistula was doubly tied and cut between the ties. The lower segment of the esophagus was brought out and sutured to the skin. The patient lived one hour.

Postmortem examination showed marked bilateral pneumonia and, as associated anomalies, Meckel's diverticulum and bilateral stenosis of the ureters with hydro-nephrosis.

CASE 5—O F, a boy, entered the hospital Oct 29, 1930, at the age of 4 days, with a typical history of attacks of cyanosis, choking and an excessive amount of mucus in the mouth and larynx. Roentgen studies with barium sulfate had been made at another hospital, and atresia of the upper end of the esophagus had been demonstrated. The child was well developed but poorly nourished and in considerable respiratory difficulty. Coarse rales were heard throughout both lungs, and roentgenograms showed aspiration pneumonia and gas in the stomach and intestines.

On October 30 exploration of the mediastinum was made through the posterior extrapleural approach (Dr C G Minter). The upper segment of the esophagus ended blindly about 2 cm above the bifurcation. The lower segment of the esophagus communicated with the trachea just above its bifurcation. The anomaly was of type 3b. The fistula was doubly tied and cut between the ties. The lower segment of the esophagus was freed, brought out and sutured to the skin. The patient lived fifty-six hours. Postmortem examination showed bilateral pneumonia and congenitally cystic kidneys.

CASE 6—E M, a boy, entered the hospital April 28, 1931, at the age of 4 days, with a history of regurgitation of all fluid taken by mouth. There had been no choking or cyanosis. The day before entrance he had several convulsions. He was a poorly nourished, dehydrated infant. Respirations were labored and difficult, and there were signs of bilateral pneumonia.

He improved slightly after a transfusion and parenteral fluids had been given, and on April 29 exploration of the mediastinum was done through a posterior extrapleural approach, but the patient died just as the mediastinum was exposed (Dr G D Cutler).

Postmortem examination showed a tracheoesophageal fistula. The anomaly was of type 3b. There were also bilateral pneumonia, bilateral otitis media and meningitis.

CASE 7—J V, a boy, entered the hospital Sept 3, 1932, at the age of 1 day, because of an imperforate anus.

As roentgen examination showed that the blind distal end of the sigmoid flexure was too high to reach from a perineal incision, a sigmoidostomy was done. The baby did well, but on the following day, on an attempt to pass a Levine tube, atresia of the esophagus was discovered. Roentgen studies with a catheter and

injection of iodized poppyseed oil showed that the upper segment of the esophagus ended in a blind pouch. There was a fistula between the lower segment of the esophagus and the trachea, as demonstrated by the gas in the bowel. The anomaly was of type 3b. The patient had an aspiration type of pneumonia and died on the third day. No postmortem examination was made.

CASE 8—J B, a boy, entered the hospital Dec 2, 1932, at the age of 7 hours, because of an imperforate anus. As the blind end was too high to reach from a perineal incision, a sigmoidostomy was done on December 3. It was noted at the time of operation that the infant had considerable difficulty in breathing, and there were several attacks of cyanosis, which were relieved on suction of material from the mouth and throat.

In spite of the previous case, the possibility of tracheoesophageal fistula was not seriously considered until the following day, at which time roentgen studies showed complete obstruction of the upper segment of the esophagus and a large amount of gas in the stomach and intestines. On exposure (Dr W E Ladd) of the posterior mediastinum a tracheoesophageal fistula (type 3b) was found, but the patient died on the table. No postmortem examination was made.

CASE 9—R H, a boy, entered the hospital Feb 13, 1933, at the age of 3 days, with a typical history of regurgitation of all fluid given by mouth, at which times there were attacks of cyanosis. Roentgen studies with barium sulfate at another hospital had shown an obstruction of the upper segment of the esophagus. On admission the lungs showed some evidence of pneumonia, due in part at least to the barium sulfate, which had been aspirated into the lung.

On February 13 the mediastinum was explored through the posterior extrapleural approach (T H L). The lower segment of the esophagus was identified and found to enter the trachea at its bifurcation. The anomaly was of type 3b. Two ties were placed about the fistula and cut between. The lower segment of the esophagus was freed, a soft rubber catheter was inserted, and the esophagus was brought out and sutured to the external wound.

The child did fairly well for nine days, but it was obvious that some effort must be made to exteriorize the upper end of the esophagus, because of the difficulty in preventing aspiration of the contents of the upper blind pouch. On February 25, through an anterior incision in the neck, the upper segment of the esophagus was freed, brought out through the neck and stitched to the wound. Its lower blind end was opened, and a small soft rubber catheter was inserted. This patient lived three days after the second operation and fifteen days after the first operation.

Postmortem examination showed bilateral pneumonia and some mediastinitis. In this case it was felt that a better exposure of the mediastinum was obtained by resecting the third, fourth, fifth and sixth ribs instead of the fourth, fifth, sixth and seventh ribs as in the previous instances. (See text for description of methods advised at present.)

CASE 10—M C, a girl, entered the hospital Aug 13, 1933 at the age of 2 days, with a typical history of regurgitation of all liquid taken by mouth. There had also been several attacks of choking and cyanosis.

Roentgen studies with barium sulfate at another hospital demonstrated a blind upper segment of the esophagus, and there was barium sulfate throughout the entire bronchial tree. Roentgen examination here showed a large amount of gas in the stomach and intestines and some infiltration of the lungs. After parenteral fluids had been given, exploration of the mediastinum through the posterior extrapleural

approach was done on August 13 (T H L) The lower segment of the esophagus was found to communicate with the trachea at its bifurcation The anomaly was of type 3b The fistula was doubly tied and cut between the ties A catheter was inserted in the lower segment of the esophagus This lower segment was freed and brought out through the wound The patient died twelve hours after the operation

Postmortem examination showed bilateral pneumonia and bilateral pleurisy In addition there were Meckel's diverticulum and an interventricular septal defect of the heart, and there was no gallbladder Fluid from the chest grew *Staphylococcus aureus* In this case there was a rather wide separation (3 cm) between the upper and the lower segment of the esophagus

CASE 11—M L, a girl, entered the hospital Sept 22, 1933, at the age of 15 days. As usual there was a history of an excessive amount of mucus coming from the mouth, and there had been attacks of choking and cyanosis whenever liquids were offered. Roentgen studies with barium sulfate at another hospital had demonstrated a blind end of the upper segment of the esophagus

On September 23 the mediastinum was explored through a posterior extrapleural approach (T H L) The third, fourth, fifth and sixth ribs were sectioned just to the right of the transverse processes, and about 1 inch (2.5 cm) of each of these ribs was resected The pleura was pushed laterally, and the mediastinum was entered. The lower segment of the esophagus communicated with the trachea at its bifurcation. The upper segment ended blindly The anomaly was of type 3b The fistula was doubly tied and cut between the ties A soft rubber catheter was inserted in the lower segment of the esophagus which was freed, brought out through the wound and sutured to the skin

The child stood the operation fairly well, and four days later (September 27) the upper segment of the esophagus was freed, brought out and sutured to the cutaneous wound of the neck Its blind end was opened, and a catheter was inserted for drainage.

On September 30, seven days after the first operation, it was found that the opening of the lower segment of the esophagus had become detached from the cutaneous wound It had retracted within the posterior thoracic wound, and it was no longer possible to introduce food through its opening

On October 1 the posterior wound was opened, and the lower end of the esophagus was found and tied It could not be brought out to the surface of the skin, as it had retracted and was adherent It was felt that an attempt to free it would lead to further infection A drain was replaced in the posterior wound, and an anterior gastrostomy was then done For about two weeks after the anterior gastrostomy, the child did well and gained weight She then had diarrhea, signs of bilateral pneumonia appeared, her course became downhill, and she died on October 23, at the age of 47 days Death occurred twenty-five days after the third procedure and thirty-two days after the first operation

Autopsy showed bilateral pneumonia, moderate mediastinitis, bilateral otitis media (*Staph. aureus*), bilateral hydronephrosis and stricture of the right ureter at the ureteropelvic junction

CASE 12—M B, a girl, entered the hospital Dec 14, 1933, at the age of 2 days, with a history of attacks of cyanosis, dyspnea and choking There was also an excessive amount of mucus coming from the mouth, which was relieved by suction An attempt to pass a catheter showed an obstruction to the esophagus Roentgenograms showed gas in the stomach and intestines and also considerable infiltration of both lungs and a probable aspiration type of pneumonia.

On December 14, exploration of the mediastinum was done through the posterior extrapleural approach (Dr W E Ladd). The lower segment of the esophagus was found to communicate with the trachea. The anomaly was of type 3b. The fistula was doubly tied and cut between the ties. The lower segment of the esophagus was brought out through the wound, a catheter was inserted, and the esophagus was sutured to the skin. The patient died eight hours after the operation. No autopsy was performed. It is interesting to note that this patient's older brother had the same congenital anomaly (case 8).

CASE 13—P S, a girl entered the hospital Jan 1, 1934, at the age of 11 days, on account of attacks of cyanosis, dyspnea and choking since birth whenever fluid was offered by mouth. The baby weighed only 3 pounds (1,307 Gm), and there was roentgen evidence of bilateral pneumonia. A catheter met an obstruction in the esophagus at about the level of the second dorsal vertebra.

On January 2, exploration of the mediastinum through the posterior extrapleural approach was done (T H L). The fourth rib was resected for about 2 inches (5 cm), and the third and fifth ribs were cut close to the transverse process. The lower segment of the esophagus was found to communicate with the trachea at its bifurcation. The anomaly was of type 3b. There was better exposure of the site of the fistula than in any previous case. On account of the poor condition of the child, a double tie was placed about the fistula and cut between. It was planned to do an anterior gastrostomy later. However, the child died three hours after the operation. No autopsy was performed.

CASE 14—J T, a boy, entered the hospital Sept 4, 1934, at the age of 2 days, with a typical history of attacks of choking, vomiting and cyanosis whenever fluid was given. Between attacks there was an excessive amount of mucus coming from the mouth. At another hospital a catheter had been passed, and complete obstruction of the esophagus had been demonstrated.

On admission scattered rales were heard throughout both lungs, the baby was poorly developed and poorly nourished and weighed only 5 pounds (2,268 Gm). A catheter was passed down the esophagus, and an obstruction was met at the level of the first thoracic vertebra. There was no air demonstrable in the stomach or in the intestines. It was felt that the child had atresia of the esophagus, type 2, that is, both segments of the esophagus ended blindly. Two hours after admission the child had a severe attack of cyanosis, and respirations ceased.

Postmortem examination showed that the upper and lower segments of the esophagus were separated by about 5 cm, though there was a fine fibrous cord connecting the two. On careful dissection the upper segment of the esophagus was found to have a pin-sized fistula connecting it with the trachea. The anomaly, then, should be classified as type 3a and not type 2. There was marked bilateral pneumonia. Culture from the heart's blood and peritoneum showed *Staphylococcus albus haemolyticus*.

This mistake in diagnosing the type of anomaly is probably not of importance as regards surgical treatment. The fistula was so small that it is unlikely that there was any aspiration of material through it from the upper segment. No air had passed through it.

CASE 15—J C, a boy, entered the hospital on March 7, 1935, at the age of 1 day, with a typical history of cyanotic attacks occurring a few minutes after birth, which were relieved on suction of mucus from the mouth. These attacks continued, and on admission there was a very severe one. The lungs showed evidence of consolidation, and coarse rales were heard throughout both sides of the chest. Roentgenograms taken after passing a catheter showed the upper segment



of the esophagus to end blindly at about the level of the second dorsal vertebra, and there was considerable gas in the bowel. The child died a few hours after admission, no operation having been performed.

Postmortem examination showed a tracheoesophageal fistula of type 3b, bilateral bronchopneumonia of the aspiration type, atresia of the right ureter, Meckel's diverticulum and otitis media (*Staph aureus*).

CASE 16—M C, a girl, entered the hospital Jan 1, 1936, at the age of 2 days. There had been difficulty with breathing since birth and regurgitation of all fluid taken by mouth. On entrance there was some diminished resonance over the left side of the chest, and many coarse rales were heard in both lungs. A catheter passed down into the esophagus met an obstruction at the level of the second dorsal vertebra. There was considerable gas in the stomach and intestines.

On January 2, an exploration of the mediastinum through the posterior extrapleural approach was done (T H L). About  $1\frac{1}{2}$  inches (37 cm) of the fourth rib was resected, and the third and fifth ribs were sectioned close to the transverse processes. In pushing the pleura laterally a small hole was made in it. Good exposure was obtained. The upper segment ended blindly, and the lower segment of the esophagus was found to communicate with the trachea just above the bifurcation. The anomaly was of type 3b. The fistulous tract was doubly tied and cut between the ties. The upper and lower segments were then freed, both ends were opened, and an end to end anastomosis was performed with interrupted mattress sutures of fine silk. The wound was closed, a small rubber drain being left down to the mediastinum. The child's condition was good at the start but was rather poor at the end of the procedure, and he died three hours after the operation.

Postmortem examination showed bilateral acute bronchitis and a moderate amount of pulmonary atelectasis. The anastomosis appeared to be tight and not under undue tension.

CASE 17—J N, a boy, entered the hospital April 24, 1936, at the age of 4 days, because of persistent vomiting and regurgitation of everything taken by mouth and attacks of choking occasionally associated with cyanosis. Many coarse rales were heard throughout both lungs. Roentgen examination showed that the catheter passed down the esophagus met an obstruction at about the level of the second dorsal vertebra. There was a large amount of gas in the stomach and intestines, and there was also considerable infiltration in both lungs.

On April 25 the mediastinum was explored (Dr W E Ladd) through the posterior extrapleural approach, and in this case 2 inches (5 cm) each of the third, fourth, fifth and sixth ribs was removed. The lower segment of the esophagus was found to communicate with the trachea at the bifurcation. The upper end was blind. The anomaly was of type 3b. The fistula was ligated and cut, the lower segment of the esophagus was freed and brought out through the wound after a catheter had been placed in the esophagus.

The patient died two hours after operation. No autopsy was performed.

CASE 18—C L, a boy, entered the hospital June 14, 1936, at 8 days of age, because of regurgitation associated with attacks of cyanosis and choking on attempted feeding. Roentgen studies with barium sulfate at an outside hospital showed atresia of the upper segment of the esophagus. On admission roentgen examination showed considerable infiltration of both lungs and evidence of aspiration pneumonia, there was a considerable amount of barium sulfate in the bronchial tree. A large amount of gas was seen in the stomach and intestines, and it was presumed that the anomaly was of type 3b.

On June 14, the mediastinum was explored through a posterior extrapleural approach, with resection of a portion of the fourth and fifth ribs, the third and sixth ribs being sectioned close to the transverse processes (T H L). Good exposure of the mediastinum was obtained. The upper segment of the esophagus was not seen. The lower segment of the esophagus communicated with the trachea at the bifurcation. The fistulous tract was doubly tied and cut between the ties. After a catheter had been placed in the lower segment of the esophagus, it was freed and brought out through the wound. The child did fairly well, but, on account of the constant aspiration of mucus from the upper segment, on June 25, ten days later, the upper segment of the esophagus was dissected as far as possible, doubly tied, cut between the ties and sutured to the skin on the anterior surface of the neck. In this case complete dissection of the upper segment was not accomplished. On June 29, it was found that the lower segment of the esophagus had separated from the cutaneous wound and had retracted within the chest.

On June 30, an anterior gastrostomy was done by the Witzel technic. The sutures and drain were removed from the anterior upper wound, and there was no evidence of infection in the neck. There was a considerable amount of saliva draining from the upper esophagostomy opening. At this same time the posterior esophagostomy wound was explored. The tissues were very friable, and there was evidence of considerable infection in this area. The open end of the lower segment of the esophagus was not seen. This posterior wound was left open with a drain. The child did fairly well for a week, after which he began to go downhill. He died on July 12.

Postmortem examination showed a rather marked degree of mediastinitis, bilateral pneumonia with multiple small pulmonary abscesses, moderate fibrinous pleuritis on the right, otitis media and peritonitis. Culture of the exudate in the right pleural cavity grew gram-negative cocci and gram-negative bacilli.

This attack on the problem brings out a number of points. This case, as well as case 11, shows that if the patient lives it is difficult to keep the exteriorized lower end of the esophagus attached to the external wound in the back. Unless the lower segment is freed for a considerable distance, the tension will cause it to retract. If it is sufficiently freed, the blood supply at its open end is probably interfered with. Also it seems clear that unless the upper segment is exteriorized the patient will continue to be in danger of having an aspiration type of pneumonia. In this instance postmortem examination showed that there had been a small fistula connecting the distal stump of the upper segment of the esophagus with the trachea. This must have been an added factor in the aspiration of the contents from the upper segment. The anomaly in this case should be classified as type 3c.

CASE 19—J T, a boy entered the hospital July 11, 1936, at the age of 2 days. All fluids given by mouth were immediately regurgitated or vomited, and there was an excessive amount of mucus coming from the mouth. There had been occasional attacks of cyanosis. On examination the child appeared in fairly good condition, though coarse rales were heard throughout both sides of the chest. Roentgen examination showed complete obstruction of the upper segment of the esophagus and considerable gas in the stomach and intestines. The anomaly was of type 3b.

On July 11, about 2 inches (5 cm) of the fourth rib was resected (T H L), and the third and fifth ribs were sectioned close to the transverse process. The intercostal muscles were separated, the pleura pushed laterally and the mediastinum entered. A small rent was made in the pleura, but this was resutured. The lower segment of the esophagus was found to communicate with the trachea at the bifurcation. The fistulous tract was doubly tied and cut between the ties, and

the lower segment was freed. The upper end was identified and freed. The two ends were cut and anastomosed with interrupted mattress sutures of silk.

The patient stood the operation fairly well. The exposure was good, and it was felt that the anastomosis had been done without tension. During the following forty-eight hours the infant's respirations became very labored, and he died seventy-two hours after the operation. No postmortem examination was made.

CASE 20—J O B, a boy, entered the hospital Nov 30, 1936, at the age of 4 days. There was a typical history of difficult breathing and attacks of cyanosis whenever liquid was offered by mouth. Examination showed a moderate degree of icterus, there were frequent mild attacks of labored breathing associated with cyanosis, and there was an excess of mucus coming from the mouth. Rales were heard throughout both lungs and some harsh breath sounds over the right lung. Roentgenograms showed that the catheter met an obstruction at the lower level of the second dorsal vertebra and that there was a large amount of gas in the stomach and intestines. The anomaly was of type 3b.

Operation was performed November 30 (T H L) with the same approach as in the previous case. The lower segment of the esophagus was found to communicate with the trachea through an unusually wide fistula. The fistula was doubly tied and cut between the ties. The lower segment was mobilized and opened, the upper blind segment was also freed and opened. An anastomosis was done with several mattress sutures of fine silk, and there appeared to be no tension on the suture line. A small rent had been made in the pleura, but this was closed. A rubber drain was left in the mediastinum, and the wound was closed.

This patient lived eight days and at the end of this time, perhaps unwisely, the patient was given a small amount of sterile saline solution by mouth, which was swallowed easily. The following day a slight serous drainage was noted coming from the wound. This was thought to contain saliva. The same day the baby's condition suddenly became poor, there was circulatory collapse, and he died on the ninth postoperative day.

Postmortem examination in this case was rather discouraging in that it showed a leak at the site of the anastomosis. It was felt that this was due to tension at the site of the anastomosis rather than a direct result of the fluid given by mouth. There was acute posterior mediastinitis, *Streptococcus haemolyticus* was isolated. There was a slight amount of fluid in both lungs, which on culture grew *Str haemolyticus*. There was bilateral pneumonia. *Str haemolyticus* was isolated from the blood stream. Meckel's diverticulum, a hemivertebra and an anomaly of the pancreatic duct were associated with the condition.

In spite of this fatality, it was felt that progress in treating this condition by the direct attack was being made. At least there was no undue operative shock, as the patient lived over a week.

CASE 21—M O'S, a girl, entered the hospital May 12, 1937, at the age of 6 days, because of attacks of vomiting, regurgitation of fluid and cyanosis since birth. There was a moderate amount of abdominal distention, and there was an ectopic anus with a narrow opening at the junction of the posterior wall of the vagina and the perineum. Both lungs showed evidence of a pneumonic process.

In spite of the poor condition of the child, an attempt was made after giving a transfusion and parenteral fluids to explore the posterior mediastinum through the extrapleural approach (T H L). When the mediastinum was entered it was found that the lower segment of the esophagus entered the trachea at a lower level than usual, appearing as a direct continuation of the trachea. The upper segment was found to end blindly, there was a rather wide separation (3 cm)

between the upper and the lower segment of the esophagus. The patient's breathing ceased before any further operative procedures were carried out.

Postmortem examination showed, in addition to the tracheoesophageal fistula (type 3b), an ectopic anus, infantile coarctation of the aorta, anomalous and rudimentary attachment of the mesentery of the bowel, acute bilateral bronchopneumonia, aspiration of amniotic sac contents and acute mastoiditis on the left. Had this patient lived an attempt would have been made only to close the fistula at that time. There was too wide a separation between the two segments to justify trying to anastomose them. Additional later procedures would have been necessary.

CASE 22—J G, a boy, entered the hospital July 26, 1937, at the age of 2 days. There had been regurgitation with some cyanosis on attempted feeding. Examination under roentgen rays at another hospital had not included the use of opaque fluid. The child was in fairly good condition. Roentgen examination at this hospital showed that the catheter met an obstruction at the fourth thoracic vertebra and that there was gas in the stomach and in the upper part of the intestinal tract. The anomaly was of type 3b.

On July 27, the mediastinum was explored through the posterior extrapleural approach (T H L). About 1 inch (2.5 cm) of each of the fourth and fifth ribs was resected, and the third and sixth ribs were sectioned close to the transverse process. This gave an excellent exposure, and the lower segment of the esophagus was found to communicate with the trachea at its bifurcation. The fistulous tract was doubly tied and cut between the ties. The lower and upper segments were then freed, and it was possible to bring them together without tension. The upper segment of the esophagus was opened at its lowest point, and the two ends of the esophagus were then anastomosed with interrupted mattress sutures of fine silk. A rubber drain was placed in the mediastinum, and the wound was closed.

The patient recovered from the operation and with administration of parenteral fluids his condition greatly improved. He was given nothing by mouth. There was a slight serous discharge from the posterior wound on the fifth day. Parenteral fluids were given daily, as well as several blood serum transfusions. On the ninth postoperative day the respirations suddenly became labored, and the child died in a very few minutes.

Postmortem examination showed that the two ends of the esophagus were approximated, and, although there was slight tension in this region, there was no evidence of leakage. The wound appeared to be healing well, and there was little, if any, mediastinitis. Cultures showed no growth. It was felt that the anastomosis had been adequately done. There was dilatation of the right side of the heart, hemorrhage in the lungs and free fluid in the serous cavities. There seemed little doubt that death was caused by too much fluid given parenterally. A constant intravenous infusion was used, and this I now realize to be very dangerous for patients of this age group. Distressing as was the result in this case, it shows that a direct attack with primary anastomosis may be successful.

CASE 23—F R, a girl entered the hospital Aug. 26, 1937, at the age of 36 hours because of an imperforate anus. Operation to correct this was done on August 27. It was noted at the time of operation that the baby had attacks of cyanosis and that there did not seem to be as much meconium in the rectum as is usual. On the second day moist rales were heard in the chest, and there were some attacks of cyanosis. Roentgen examination showed that the catheter had met an obstruction at the level of the fourth dorsal vertebra. There was a considerable amount of air in the stomach and intestines.

On August 28, the posterior mediastinum was explored through the extrapleural approach (Dr G D Cutler). The upper segment of the esophagus was found to end blindly, while an attempt was made to identify the lower end the patient's condition became very poor, and he died on the table.

Postmortem examination showed a tracheoesophageal fistula type 3b. There were also Meckel's diverticulum, marked bilateral bronchopneumonia and the post-operative repair of an imperforate anus. In view of cases 7 and 8 in which there was an imperforate anus in addition to a tracheoesophageal fistula, this condition might have been recognized sooner.

CASE 24—J G, a boy, entered the hospital Oct 1, 1937, at the age of 48 hours, with a history of repeated attacks of cyanosis and choking whenever liquid was offered. There was also a note that nothing had been passed by rectum.

On examination coarse rales were heard throughout both lungs. Roentgen examination showed that the catheter met an obstruction at the level of the first dorsal vertebra. There was no gas in the stomach or intestines. A diagnosis of esophageal atresia, type 2 (see illustration, B) was made, and it was felt that this type of anomaly in the presence of pneumonia would be better attacked by an anterior esophagostomy of the upper, blind end followed by an anterior gastrostomy. This was done on October 1 (Dr P J Mahoney). The child did fairly well at first, but on the seventh day his condition became poor, there was evidence of bilateral pneumonia, and he died on the eighth postoperative day.

Postmortem examination showed esophageal atresia of type 2, that is, both ends were blind, neither segment communicating with the trachea, and the two blind ends were separated by about 5 cm. There were bilateral pneumonia, dextroposition of the aorta and an interventricular septal defect. There was an area of erosion in the stomach, with perforation and peritonitis. This area was not associated with the gastrostomy wound, and its cause was obscure. Microscopically the wall of the stomach showed an extensive infiltrative reaction with autolysis but without evidence of inflammatory reaction. The observation in this case of cerebral cortical atrophy raises the question whether this gastromalacia might be similar to the Cushing ulcers associated with lesions in the region of the third ventricle. In only 1 other case has there been observed such a wide separation of the two segments of the esophagus.

CASE 25—M W, a girl entered the hospital July 24, 1938, at the age of 3 days, with a history of difficulty in swallowing and occasional attacks of choking. On admission the child was in rather poor condition. Roentgen examination with a catheter passed down the esophagus showed that the upper end of the esophagus ended blindly and that there was a large amount of gas in the stomach and intestines. There was pneumonic infiltration in both lung fields. Operation, performed on July 24 (Dr P J Mahoney), consisted in exploration of the mediastinum by the transpleural approach. The patient died just as the mediastinum was entered. Post-mortem examination showed marked pneumonia on both sides and a tracheoesophageal fistula of type 3b. It appeared as though the two segments were close enough to permit anastomosis. In addition there were dextroposition of the descending thoracic aorta, a slight degree of infantile coarctation of the aorta and a patent ductus arteriosus. Death was due to surgical shock as well as to a bilateral bronchopneumonia. This was the first attempt in this hospital of a transpleural approach to the mediastinum.

CASE 26—M H, a girl, entered the hospital Dec 26, 1938, at the age of 1 day, because of an imperforate anus and occasional attacks of cyanosis. Roentgen examination showed a pneumonic process in both lungs. A catheter was not

passed down the esophagus. There was a collection of gas in the upper portion of the abdomen, which gave the appearance of obstruction of the duodenum with dilatation of the stomach and duodenum. There was no gas in the intestines distal to the duodenum. No estimate could be made of the extent of the intestinal atresia.

On December 27, an abdominal exploration was made (T H L). Duodenal atresia was found, which was relieved by a side to side duodenojejunostomy. The remainder of the intestinal tract seemed patent. On the next day, operation for imperforate anus was undertaken. The rectum was easily freed, opened and sutured to the edge of skin without tension. The child died within twelve hours after the second operation. Postmortem examination showed, in addition to the findings already known, a tracheoesophageal fistula of type 3b. There was extensive bilateral bronchopneumonia. There were an interventricular septal defect of the heart and almost complete stenosis of the right ureter. The two operative procedures for the two recognized lesions seemed adequate.

CASE 27—J F, a girl, entered the hospital on March 15, 1939, at the age of 3 hours, on account of an imperforate anus. Attacks of slight cyanosis had been noted soon after birth. On admission the respirations were labored, but nothing abnormal was noted in the chest. There was no anal opening. There appeared to be a bifid scrotum, above which was a rudimentary structure thought to be a penis or possibly the clitoris. No testes were felt. On account of increasing cyanosis an attempt was made to suction fluid from the mouth, but it was found that a catheter could not be passed into the stomach. There was much gas in the stomach and intestines. In view of the experience in other cases of tracheoesophageal fistula associated with an imperforate anus, it seemed rational to attack the fistula first, as the more urgent anomaly.

On March 15, the mediastinum was exposed (T H L) through a transpleural approach between the fourth and fifth ribs. The posterior mediastinum was entered. The lower segment of the esophagus was found to enter the trachea just above its bifurcation, and the blind upper segment was found 1 cm. above it. Both ends were freed, and an anastomosis was performed with interrupted mattress sutures of silk, but before this operation could be completed the patient died.

Postmortem examination showed that the anastomosis was well performed and not under tension, but, of course, whether it would have remained tight cannot be stated. In addition there was the known atresia of the rectum, there were also a bicornuate uterus, a patent ductus arteriosus, a persistent cloaca, a cystic left kidney and hyperplasia of the clitoris. In this case, as in case 27, there seemed to be considerable shock associated with the transpleural approach.

CASE 28—J K, a boy, entered the hospital May 20, 1939, at the age of 2 days, with a typical history of regurgitation of large amounts of mucus, attacks of cyanosis and choking spells associated with the giving of fluid by mouth. There was also marked abdominal distention, and nothing had been passed by rectum. A diagnosis of intestinal obstruction in addition to a probable tracheoesophageal fistula was made.

Abdominal exploration (T H L) showed that the small intestine was dilated and gangrenous from about 8 inches (20.3 cm.) below the ligament of Treitz to just distal to the ileocecal valve. The bowel was obviously not viable. Resection and anastomosis between the remaining small intestines and the ascending colon were done. In view of the tracheoesophageal fistula, the cardiac end of the stomach was then ligated, and a gastrostomy was performed below this ligation. In spite of these heroic measures, the justification for which is debatable, the patient did not die until the third postoperative day.

The postmortem observations, in addition to the conditions noted at operation, were a tracheoesophageal fistula of type 3b, bilateral pneumonia, bilateral pleuritis, some pulmonary edema, cerebral congestion, coarctation of the aorta, stenosis of the right ureter and bifid pelvis of the left kidney. The cardiac end of the stomach was well closed. There was some free fluid in the peritoneal cavity, but there was no peritonitis.

CASE 29—Y O, a girl, entered the hospital Aug 20, 1939, at the age of 6 hours, because of repeated attacks of cyanosis. The child weighed 3 pounds 8 ounces (1,533 Gm.) and was in poor condition. At entrance it was felt that some intracranial injury might explain the symptoms, and it was not until the third day that a tracheoesophageal fistula was suspected and demonstrated. There had not been any attack of vomiting, and, although the fluid given by mouth was regurgitated, it was felt that this was merely an evidence of inability to suck.

Roentgen examination showed obstruction in the esophagus with air in the stomach. The anomaly was of type 3b. On account of the poor condition of the child it was decided to attempt the procedure advocated by Gage and Ochsner,<sup>4</sup> as in case 28. Through an abdominal incision the cardiac end of the stomach was tied, and a small catheter was sewed in the fundus of the stomach. The child's condition remained poor, and she died twenty-four hours after the operation. No autopsy was performed.

CASE 30—W M, a boy, entered the hospital Aug 20, 1939, at the age of 3 days, with the history that there had been an excessive amount of mucus coming from the mouth, with vomiting and attacks of cyanosis and choking on attempts at feeding. Coarse rales were heard throughout both sides of the chest. Roentgen examination showed that the catheter met an obstruction at the third dorsal vertebra, and there was considerable gas in the stomach and intestines.

Operation was done on August 21 (T H L). Through an abdominal approach the Gage Ochsner procedure was used. The cardiac end of the stomach was tied, and a gastrostomy of the Witzel type was performed. After the operation the patient continued to have cyanotic spells in spite of constant efforts to keep the upper segment of the esophagus free of secretions. These increased in severity, and on the third postoperative day the child died during an attack.

At autopsy there were bilateral pneumonia and peritonitis probably due to leakage above the gastric tube. The tracheoesophageal fistula was of type 3b.

CASE 31—C R, a girl, entered the hospital Jan 16, 1940, at the age of 3 days. There was the usual history of attacks of cyanosis and vomiting immediately after feedings were attempted. She appeared to be a mongol, weighed only 4 pounds (1,814 Gm.) and was in poor condition. There was evidence of involvement of both lungs. A catheter passed down the esophagus met an obstruction at the level of the second dorsal vertebra, and there was considerable gas in the stomach and intestines. It was decided to attempt the procedure suggested by Gamble.<sup>8</sup> The abdomen was opened (T H L), and the stomach was cut entirely across at the junction of the upper and middle third. The upper end was sutured to the upper end of the wound to allow free drainage of the lower segment of the esophagus. The lower part of the stomach was closed, and a catheter was introduced in this lower segment by the Witzel technic. The patient lived only eighteen hours.

Autopsy showed bilateral pneumonia, bilateral pleurisy, a patent foramen ovale and a horseshoe kidney with three ureters. There was no peritonitis, and the

<sup>8</sup> Gamble, H A. Tracheo-Esophageal Fistula, *Ann Surg* 107 701, 1938.

gastrostomy openings seemed tight. However, it was too soon after operation for this to be significant.

CASE 32—H. G., a boy, entered the hospital Feb. 8, 1940, at the age of 1 day. There had been a large amount of mucus coming from the mouth, but there had been no cyanotic attacks. It was noted that the child had an imperforate anus, and there was a history of meconium being passed from the bladder. Roentgen examination showed that a catheter passed down the esophagus stopped at the level of the second dorsal vertebra. There was gas in the stomach and bowel. A film taken in the upside-down position showed that the gas in the blind end of the sigmoid flexure was at the brim of the pelvis.

Operation was performed on February 8 (T. H. L.). A tube was placed in the lower blind end of the sigmoid flexure. The large bowel was greatly dilated with meconium, some areas of the bowel wall were very dark, but it seemed viable. The sigmoid flexure was sutured to the peritoneum about the tube, and the wound was closed. An upper left rectus incision was then made, and a very small stomach was delivered into the wound. It was cut across at the junction of the upper and middle third as suggested by Gamble.<sup>8</sup> The distal end of the stomach was then closed, and a catheter was inserted and sutured in the distal segment for feeding. Instead of attempting to suture the opened cardiac end of the stomach to the wound, the cardia was closed except for about  $\frac{1}{2}$  inch (1.2 cm.) on the greater curvature, where a catheter was inserted up into the esophagus and sutured in place. This step is a modification of both the Gamble<sup>8</sup> and the Leven<sup>9</sup> procedure. The upper gastrostomy tube was sutured to the upper end of the wound, the peritoneum was brought together in the middle of the wound, and the lower gastrostomy tube was sutured to the lower end of the wound. Muscle, fascia and skin were sutured between the two catheters. The liver interfered considerably with the delivery of the stomach in this case. The child died forty-eight hours after the operation, and postmortem examination showed that the tubes were not leaking but that there was some blood in the peritoneal cavity, and there appeared to be early peritonitis. There were bilateral pneumonia and collapse of the upper lobe of the right lung. The tracheoesophageal fistula was of type 3b.

#### COMMENT

Although Richter<sup>10</sup> in 1913 advocated a direct attack on the posterior mediastinum, with exposure of the esophagus and trachea, this was considered a procedure of too great magnitude for an infant, and even today there are many who feel that this is so.

In 1929 there was the first attempt at this hospital of any procedure other than a gastrostomy. In case 1, Dr. C. G. Mixer exposed the mediastinum through a posterior extrapleural approach. This approach had been successful in draining the mediastinum in a previous case of purulent mediastinitis caused by a foreign body perforating the esophagus. In cases 1 and 2 the attempt was successful in closing the fistula and in bringing the lower segment of the esophagus out through the back to

<sup>9</sup> Leven, N. L. Surgical Management of Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula, *J. Thoracic Surg.* **6** 30, 1936.

<sup>10</sup> Richter, H. M. Congenital Atresia of the Esophagus. An Operation Suggested for Its Cure, *Surg., Gynec. & Obst.* **17** 397, 1913.



be used for feeding. In both instances, however, the patient died almost immediately after the operation. In case 3 the same procedure was used, and the child lived for twelve hours, and in case 5 the patient survived for thirty-six hours.

In 1933 the posterior approach was used in case 9, the fistula was closed and the lower segment of the esophagus exteriorized. The infant survived nine days, at the end of which time the upper segment of the esophagus was exteriorized through an anterior incision in the neck. This patient lived fifteen days after the first operation and three days after the second.

In case 11 the posterior approach to the mediastinum was made, the fistula was tied, the lower segment of the esophagus was exteriorized to the back, and four days later the upper segment of the esophagus was exteriorized through an anterior incision in the neck. Seven days later an anterior gastrostomy was done, and at the same time the posterior esophagostomy was closed. The patient lived twenty-five days after the third operative procedure and thirty-two days after the first operation. This case offered some encouragement, although it was realized that had the child survived there would still have been the problem of connecting the openings of the "upper esophagostomy" with the anterior gastrostomy.

With increasing experience a better and better exposure of the posterior mediastinum was obtained, and it was possible to do this without making extensive tears in the pleura. The operative procedure then consisted in subperiosteal resection of the third and fourth ribs for a distance of about  $1\frac{1}{2}$  to 2 inches (3.7 to 5 cm), and section of the ribs above and below close to the transverse processes, the pleura being pushed laterally and the mediastinum entered.

Case 16 (1936) represents the first attempt at direct anastomosis through the extrapleural approach of the upper and lower segments after the fistula had been tied. This was successfully done, but the patient died a few hours after the operation. In case 18 a posterior esophagostomy of the lower segment after closure of the fistula was done. One week later the upper segment was exteriorized through an anterior incision in the neck. Four days later an anterior gastrostomy was done as in case 11. The lower segment of the esophagus had separated from the posterior cutaneous wound and had retracted within the chest. This patient died twenty-eight days after the first operation and thirty-six days after birth. (See report of case 18.)

In case 19, direct anastomosis after tying the fistula was tried again. In this instance the patient lived seventy-two hours after operation. In case 20 the same procedure was used, and the patient lived eight days. (See report of case 20.)

The operation in case 22 (1937) was the most nearly successful of all. A posterior extrapleural approach was used, the fistula was closed,

and an anastomosis of the upper and lower segments was performed. The infant lived nine days, and postmortem examination suggested that death was due solely to overhydration with parenteral fluid (See report of case 22 )

The extrapleural approach required a good deal of time, so that in case 25 a transpleural approach to the mediastinum was used as practiced by Churchill<sup>11</sup>. The patient, however, was not in good condition and died of surgical shock on the table. The condition in case 26 was hopeless, as duodenal atresia and an imperforate anus were also present. In case 27 there was an imperforate anus as well as atresia of the esophagus. In case 28 there was atresia of the ileum with extensive gangrene of the midgut, due probably to a volvulus. The condition in this case was hopeless.

The discouraging results in these last 6 cases led in 1939 to the use in cases 29 and 30 of the procedure suggested by Gage and Ochsner<sup>4</sup>. Both patients died. It is felt that ligation of the cardiac end of the stomach will not accomplish its purpose, as secretions in the lower esophageal segment still can and do drain into the trachea.

In cases 31 and 32 the procedure advocated by Gamble<sup>8</sup> was used, though in case 32 this was modified somewhat after the manner suggested by Leven<sup>9</sup>. That is, the stomach was divided and the gastrostomy tube placed in the distal segment for feeding, and the upper segment of the stomach was exteriorized to allow material in the esophagus to drain to the outside. We were unsuccessful in both cases, again the child in case 32 had in addition to the tracheoesophageal fistula and imperforate anus.

#### CONCLUSIONS

From the foregoing comments certain conclusions seem justified. Anterior gastrostomy is futile except in cases of anomalies of type 2 and type 3a, that is, it is futile unless the lower segment does not communicate with the trachea. These types are rare, each occurred only once in this series, and it is important to point out that the anomaly in case 14 was thought to be of type 2, but there was in fact a communication with the trachea from the upper esophageal segment, that is, type 3a. Differentiation between type 2 and type 3a is difficult or impossible even if an opaque medium is used at roentgen examination.

Regardless of what procedure is used for the lower segment (other than a direct anastomosis), the upper segment must be treated in some way to prevent aspiration of the overflow secretions from this blind pouch. Constant suction, in my experience, is dangerous, and Leven<sup>9</sup> has also called attention to this. Early exteriorization of this upper segment has been advocated and practiced here without success, though it is possible

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11 Churchill, E. D. Personal communication to the author.

that it would have been successful in cases 9, 11 and 18 had a posterior esophagostomy not been added to the closure of the fistula at the time of the first operation. Exteriorization of the upper segment commits the patient, if he survives, to some form of permanent exterior esophagus.

Treatment of the lower segment except in the very rare type 2 and type 3a anomalies must include measures to prevent contents from the lower segment from entering the trachea. The procedure suggested by Gage and Ochsner,<sup>4</sup> in my experience, does not do this, as tying the cardia leaves undrained (except into the trachea) the secretions of this lower segment. The procedures suggested by Gamble<sup>3</sup> and Leven<sup>5</sup> allow, in theory, free drainage of the secretions of the lower segment of the esophagus. But some method of caring for the secretion from the upper segment is necessary as well as later procedures for constructing an exterior esophagus.

In my experience these methods of Gamble and Leven directed toward exterior drainage of the lower segment have definite disadvantages and dangers. After the procedure is done, if the infant is placed with the head up to allow dependent drainage of the lower segment, the upper segment fills, and the secretions will overflow into the trachea. If the patient is placed with the head lowered, drainage of the upper segment is facilitated, but secretions from the lower segment are allowed to gravitate through the fistula into the trachea. Also, in the 2 cases in which these procedures were used it was noted that there was increased respiratory difficulty, which was thought to be due in part to free escape of the inspired air through the tracheal fistula and out the exteriorized lower segment of the esophagus.

In cases 9, 11, and 18, in which the patients lived fifteen, thirty-two and twenty-eight days respectively after the first operative procedure, it is possible that had the first operation been that of only tying the fistula, instead of in addition freeing the lower segment and suturing it to the back to serve as an esophagostomy for feeding, a recovery might have resulted, though the construction of the undesirable external esophagus would still have been required. In my experience this lower posteriorly exteriorized segment will retract within the chest if not sufficiently freed. If sufficiently freed, the suture line holding the open end to the skin of the back will slough, because the blood supply of the mobilized segment of the esophagus has been interfered with. When such sloughing occurs, mediastinitis is probably unavoidable. Posterior esophagostomy should be abandoned.

No method of attack that does not have as its first step direct closure of the fistula between the lower segment and the trachea has any reasonable chance of success, particularly as regards a primary anastomosis, which is the goal of surgical endeavor in this condition. Direct exposure of the site of the fistula by the extrapleural approach is by no means as

formidable a procedure as has been thought. Indeed, with increasing experience and improvement in technic and anesthesia, it seems to involve less shock—certainly no more—than the methods that include a gastrotomy with anterior drainage of the lower segment of the esophagus.

#### EXTRAPLEURAL APPROACH TO THE MEDIASTINUM

The patient lies on his face with the head slightly lowered and the right arm extended over the head. The cutaneous incision starts at the level of the first and second ribs, just to the right of the spine and over the transverse processes. This incision runs downward and parallel to the spine to about the level of the fifth rib, where it begins to curve laterally below the scapula and is continued to about the posterior axillary line. The presenting muscles are sectioned and the thoracic cage exposed. The erector spinae muscles are partially sectioned at the level of the fourth rib and pulled medially. The fourth rib is resected subperiosteally for about  $1\frac{1}{2}$  to 2 inches (3.7 to 5 cm), starting close to the transverse process. The third and fifth ribs are cut subperiosteally close to the transverse processes. If more room is needed, the sixth rib and occasionally the second may be so treated. A horizontal incision of the intercostal muscle is made just above the bed of the fourth rib, starting from the transverse process and carried laterally for about 2 inches (5 cm). At the medial end of this incision the intercostal muscles between the third and fourth ribs and between the fourth and fifth ribs are sectioned by vertical incisions. The fourth and usually the third and fifth intercostal nerves have to be sectioned. The horizontal incision is then widened by freeing the muscles from the underlying pleura. With gentleness and care this can be readily done without tearing the pleura.

Starting close to the spinal column, the pleura is pushed laterally and forward so that the mediastinum can be entered. The first landmark is the azygos vein, which will be seen crossing the field horizontally and dorsal to the level of the bifurcation of the trachea. This vein is doubly ligated and cut between the ligatures. Careful exploration of the fatty and areolar tissue adjacent to the bodies of the vertebra will bring into view the lower segment of the esophagus. It is readily identified and freed unless, as in case 25, there happens to be dextraposition of the aorta. The fistula, which is almost invariably at the bifurcation of the trachea, is identified, it is doubly tied with silk close to the trachea and a cut is made between the ties.

The upper segment of the esophagus is usually to be found just above and dorsal to the bifurcation of the trachea, and it must now be decided whether to proceed with any attempt to free both ends and perform an anastomosis. If the gap is too wide to allow an anastomosis without tension, it is probably futile to attempt it. I have had no experience with

the use of mechanical means, such as a tube of absorbable magnesium, to bridge this gap Churchill<sup>11</sup> has attempted such a procedure in a few cases but has stated that was not successful and that he has abandoned it

By using the extrapleural approach it is possible to drain the posterior mediastinum, and drainage is desirable. It is not feasible to drain the mediastinum when using the transpleural approach. With experience it is possible to enter the mediastinum and to perform the anastomosis without opening the pleural cavity. Although resecting one rib and sectioning two others as well as their intercostal nerves takes longer than the intercostal transpleural approach, I do not believe that it adds unduly to the respiratory difficulties after operation or that it is so severe a strain on the patient as the collapse of the right lung which is necessitated by the transpleural approach. The choice between these two approaches is still a question that further experience will help to decide. Churchill<sup>11</sup> has made several attempts via the transpleural approach, but, as in this series, there was a fatal outcome in each.

If infection occurs when the extrapleural approach is used, it is likely that there is a far better chance for it to be taken care of by the extrapleural drainage of the mediastinum. If it occurs when the transpleural approach is used, both the mediastinum and the pleural cavities are likely to be involved, and there is no feasible method of draining either at the time of operation.

Direct exposure of the site of the fistula has many advantages and should be the method of choice. With this approach the exact type of anomaly may be determined and the fistula may be closed. If the distance between the two segments is not too great, a direct anastomosis is possible, as is shown by cases 16, 19, 20 and 22. The patients in cases 20 and 22 lived eight and nine days respectively, and postmortem examination in case 22 showed that death was due to overhydration and not to infection, pneumonia or mediastinitis. That this method will eventually be successful I have no doubt.

As operative procedures in the region of the fistula between the lower segment and the trachea were done in so many cases of this series, it is not possible to give with any accuracy the average distance between the upper and the lower esophageal segment. From the figures as estimated by the operator and the figures compiled from autopsy in nonoperative cases (some of which antedate the period considered in this report) it appears that this distance varies from 0 to over 5 cm., the average distance being approximately 2 cm.

The ideal case in which to attempt a direct anastomosis is one in which the patient is seen early and in which separation of the two segments, as observed at the time of closing the fistula of the lower segment, is 2 cm. or less. In patients coming to operation late and in

poor condition or in whom there is obviously too wide a separation of the segments to justify attempted anastomosis, the procedure should be only that of closing the fistula. Then, just as soon as the infant's condition warrants, and the sooner the better, the upper segment should be exteriorized in the neck. This should be followed by an anterior gastrostomy, and again the sooner the better. Once these procedures are accomplished, months or years may be allowed to elapse before construction of an exterior tube to connect the upper esophagostomy opening with the gastrostomy opening is undertaken.

These procedures, however, are to be avoided when possible, and every reasonable risk should be taken to secure a primary anastomosis. If a direct anastomosis has been done, the problem arises of how best to meet the fluid and caloric needs of the patient until sound healing has occurred. With better understanding of fluid balance, I believe that the patient's nutrition can be maintained by intravenous dextrose and saline solutions supplemented with transfusion of either whole blood or blood serum. Case 22 showed that the danger of overhydration is perhaps as great as that of underhydration. Given another opportunity, I shall attempt to meet the patient's needs without doing a gastrostomy, though such a step can be taken if conditions warrant. A reasonably healthy infant can be maintained under an intelligent regimen of parenteral feeding for a period sufficient to allow healing.

#### ANESTHESIA

Most of these operations were done with the patient under avertin with amylene hydrate anesthesia (—80 mg per kilogram) and local infiltration with procaine hydrochloride, supplemented in some cases by oxygen and ether. Recently I have used cyclopropane as a supplement to local procaine hydrochloride anesthesia, and I believe it to be advantageous. For the use of any inhalation anesthesia a well fitting infant's face mask is essential.

#### SUMMARY

An analysis of 32 cases of congenital atresia of the esophagus is presented. In spite of the fatal outcome in all the 30 operative cases, it is felt that considerable progress along rational lines is being made. The successful operative treatment of a patient with this anomaly is only a question of time.

For a successful outcome, prompt recognition of the condition during the first few hours of life is essential. It is perhaps not advisable to go so far as to insist on routine examination of the esophagus of every infant by the passing of a catheter, as has been suggested by Gage and Ochsner,<sup>1</sup> but it is imperative that any infant who exhibits any of the characteristic signs or symptoms of esophageal atresia should at once have a catheter

passed down the esophagus, and roentgenograms should be taken without the use of any opaque medium. Once the obstruction is discovered, immediate operation should be undertaken.

An associated tracheoesophageal fistula was present in 91 per cent of this series. A direct attack on the tracheoesophageal fistula, if one is present, should be undertaken. From the experience presented here, the extrapleural approach would seem to be safer than the transpleural.

If direct anastomosis is possible, it should be done. If it is successful and no complication develops, the problem for that case is solved, barring possible esophageal stenosis later. If direct anastomosis of the two segments appears impossible or inadvisable, the tracheoesophageal fistula should be closed and nothing further done at that time. Subsequent procedures to be done just as soon as conditions permit are, first, the exteriorization of the upper esophageal segment and, second, an anterior gastrostomy. If the patient survives, construction of an exterior connection between the upper esophagostomy and the anterior gastrostomy can then be postponed until a suitable age. One must remember that an exterior esophagus as a palliative procedure for an elderly patient with cancer is justifiable and endurable, but one dreads to commit an infant to the sort of existence it entails. Every effort should be made to recognize these conditions in the first few hours of life as well as to improve surgical technic to such a degree that a direct anastomosis will be possible in an increasing number of cases.

Given a suitable case in which the patient is seen early, I feel that, with greater experience, improved technic and good luck, the successful outcome of a direct anastomosis can and will be reported in the near future.

# ROENTGEN DEMONSTRATION OF ESOPHAGEAL VARICES

## ITS CLINICAL IMPORTANCE

RICHARD SCHATZKI, M D

BOSTON

Twelve years have passed since Wolf<sup>1</sup> reported 2 cases in which he had demonstrated varices of the esophagus roentgenologically. His original observations have been confirmed and amplified by others.<sup>2</sup> In 1931 I published 5 cases and described for the first time the roentgen demonstration of varices of the stomach.<sup>3</sup> A report on 45 cases appeared three years later.<sup>4</sup> Numerous cases have since been observed by many roentgenologists. Nevertheless, a systematic and routine search for varices, particularly for those of minor degree, has not been widely practiced. In addition, the clinical importance of roentgen demonstration of varices has not received the recognition which it deserves. This is apparent when one reads publications from large teaching centers in which the differential diagnosis of splenomegaly is extensively discussed without mention of roentgen visualization of varices. It seems justifiable, therefore, to review the roentgen demonstration of varices and to discuss its clinical value.

This review is based on a series of 116 cases in which I have demonstrated esophageal varices.

The principle of roentgen visualization of esophageal varices is simple. It rests on the fact that the dilated veins bulge into the lumen and produce an uneven, wormlike surface of the inside of the esophagus. These

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From the Department of Roentgenology, the Massachusetts General Hospital

1 Wolf, G. Erkennung von Oesophagusvarizen im Röntgenbild, *Fortschr a d Geb d Rontgenstrahlen* **37** 890-893, 1928

2 Berg, H. H. Rontgenuntersuchungen am Innenrelief des Verdauungskanal, ed 2, Leipzig, Georg Thieme, 1931. Hjelm, R. Zwei Fälle von rontgendiagnostizierten Oesophagusvarizen, *Acta radiol* **12** 146-150, 1931. Kirklin, B. R., and Moersch, H. I. Report of a Case of Roentgenologically Demonstrable Esophageal Varices Complicating Splenomegaly, *Radiology* **17** 573-575, 1931. Beutel, A. Oesophagusvarizen, *Acta radiol* **12** 527-532, 1932. Oppenheimer, A. Esophageal Varices, *Am J Roentgenol* **38** 403-414, 1937.

3 Schatzki, R. Die Röntgendiagnose der Oesophagus- und Magenvarizen und ihre Bedeutung für die Klinik, *Fortschr a d Geb d Rontgenstrahlen* **41** 28-39, 1931.

4 Schatzki, R. Relietstudien an der normalen und krankhaft veränderten Speiseröhre, *Acta radiol*, 1933, supp 18, pp 1-149.



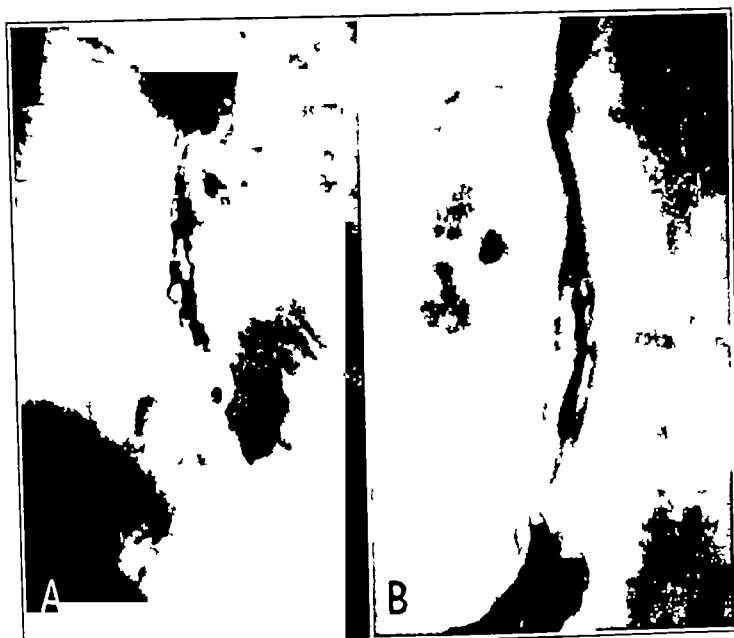


Fig 1—Extensive esophageal varices in a patient with cirrhosis of the liver  
*A*, right anterior oblique view, showing several vessels superimposed on each other  
*B*, left anterior oblique view. A large isolated tortuous vessel is demonstrated



Fig 2—Extensive varices in a patient with cirrhosis of the liver. The patient was clinically thought to have an intestinal tumor. See data in text (case 3)

protruding structures will be completely obliterated if one fills the organ with a large amount of barium sulfate. If, however, one coats the inner surface of the esophagus with only a thin layer of barium, the dilated vessels will be visible. The success of the examination depends on the technic used to obtain the desired degree of coating. This is especially true in those cases in which the varices are comparatively small.

#### TECHNIC

A watery suspension of barium sulfate serves as contrast substance. It contains equal amounts by volume of barium sulfate and water and

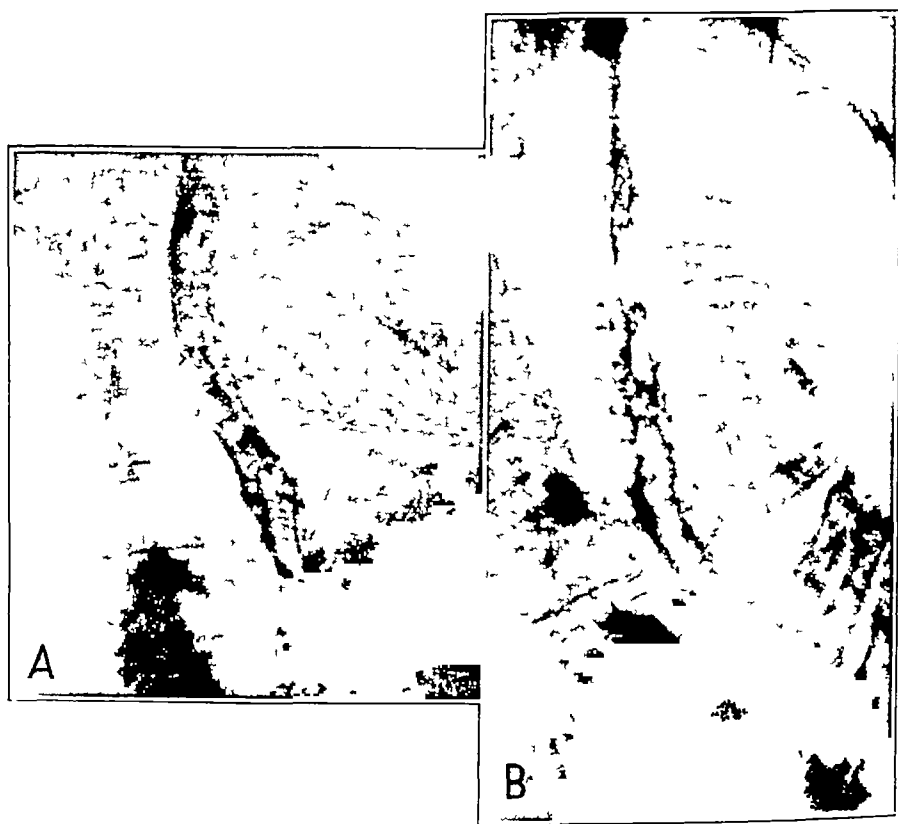


Fig 3—*A*, extensive varices in a woman with Banti's syndrome. The patient was 20 years old, with an eight year story of repeated fever, anemia and pain in the left upper abdominal quadrant. There was splenomegaly. The clinical differential diagnosis was between lymphoma and Banti's syndrome. It was decided in favor of Banti's syndrome by the demonstration of varices. Splenectomy was performed. Eight months later there was a first, gross and fatal hemorrhage. *B*, extensive varices in a patient with cirrhosis of the liver. Examination was done in order to determine the clinically uncertain source of hematemesis. There was no ascites, and the spleen was not palpable.

is the same suspension used in the routine examination of the gastrointestinal tract. Occasionally a slightly thicker mixture is required to obtain the necessary coating. The use of atropine, as previously advised,<sup>4</sup>

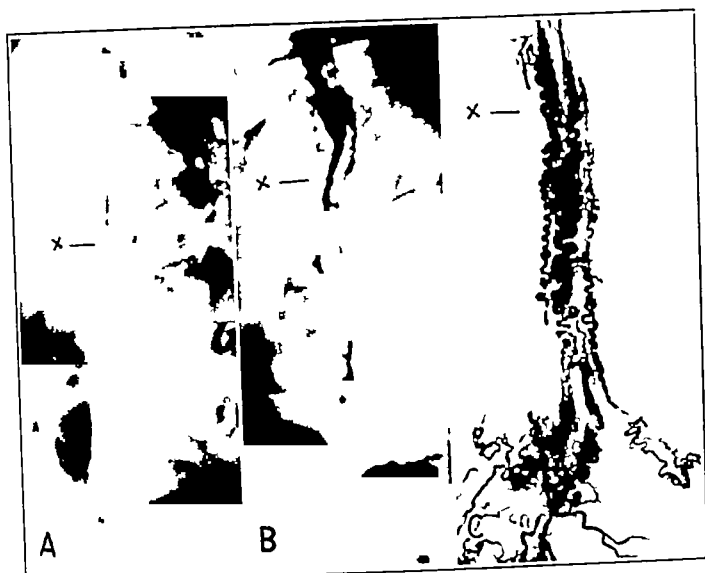


Fig 4—Extensive varices in a patient with cirrhosis of the liver *A*, complete filling of the esophagus shows widening of the organ, with localized narrowing at *x* *B*, the relief picture shows extensive varices which are superimposed on each other in the lower half of the esophagus Two large vessels are visible at *x* *C*, roentgenogram of the injected opened specimen

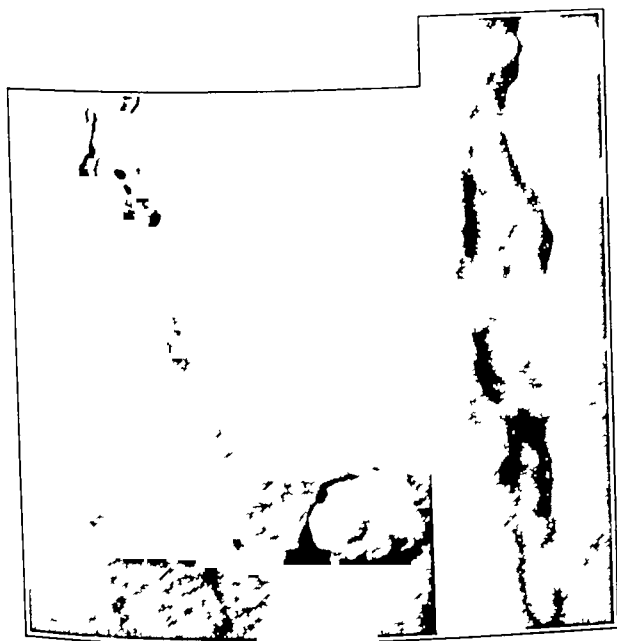


Fig 5—Marked dilatation of the esophagus due to varices in a patient with cirrhosis The varices extend through the cardia There was marked delay in the emptying of the esophagus, but no dysphagia

is rarely necessary. The moment of optimum coating is different in every case. Often it occurs at the end of deglutition, but in other instances it is obtained by waiting for a small amount of barium to flow back into the esophagus from the stomach. The latter technic is especially useful in cases of questionable small varices. The demonstrability of varices depends on a number of other factors, which will be discussed later (gravity, peristalsis, projection and respiration).

Fluoroscopic examination is of great importance in the discovery of varices. Only by this method can the optimal degree of coating of the esophagus and the optimal projections, which vary from case to case,

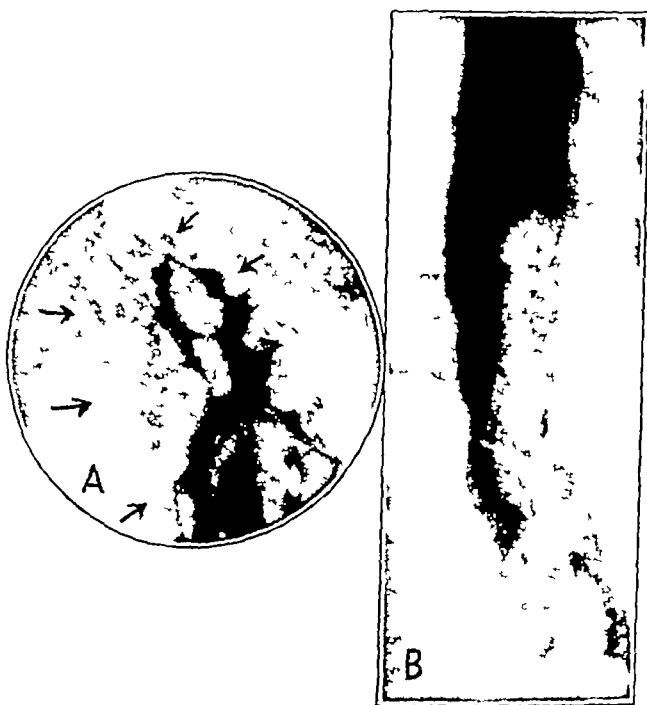


Fig 6—*A*, varices of the stomach close to the cardia (see arrows) in a patient with esophageal varices. *B*, large, tortuous, isolated vessel in the lower portion of the esophagus in a boy of 13 with Banti's syndrome. There had been a recent hemorrhage. The patient died shortly afterward from mesenteric thrombosis. Autopsy showed thrombosis of the splenic vein and of the superior mesenteric vein.

be decided. Extensive varices can easily be diagnosed during fluoroscopic study, but in the demonstration of small or questionable ones roentgenograms are indispensable. In such cases the fluoroscopic examination may give completely negative results, while the roentgenograms show the presence of varices. Roentgenograms are best taken during fluoroscopic examination (the so-called "spot," or aimed, films). Whenever the available equipment does not permit such a procedure, films

taken on the Bucky table in a projection and at an interval after deglutition determined by a preceding fluoroscopic examination will be a useful alternative

#### ROENTGEN APPEARANCE OF VARICES

Varices may be visible in a completely filled esophagus if they run along the projected edge, wherein they produce a notched or scalloped appearance. This profile picture, however, is usually not reliable. It is necessary to obtain a relief view of the varices. In the presence of varices the normal mucosal relief picture of the esophagus with its parallel longitudinal folds is changed. There results an intricate and

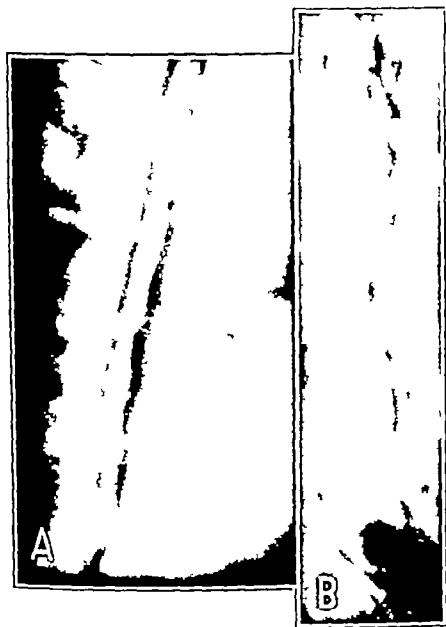


Fig 7—A, isolated enlarged vein, which is only slightly tortuous, in a case of biliary cirrhosis. B, small varicose vessels in a case of cirrhosis of the liver. The patient had his first hemorrhage two years after this examination.

often network-like pattern which is due to superimposition of the vessels bulging from the opposing walls of the esophagus (fig 4). By rotating the patient it is usually possible to demonstrate one or more isolated tortuous vessels (figs 1, 6B, 7A, 8 and 12). In a given case the dilated vessels have a definite configuration and arrangement, although their size may change considerably (see section on the influence of various factors on the demonstrability of varices).

Varices, if present, are with extremely rare exceptions located in the lower portion of the esophagus. They are often not confined to this area but may extend upward to involve the entire thoracic portion and

occasionally the cervical portion of the esophagus. However, if this is the case the esophagus immediately above the diaphragm is always involved, and the examiner should therefore concentrate on this area.

I have observed a few cases in which the varices extended into the stomach, where they produced an enlargement of the tortuous gastric folds similar to that seen in cases of localized gastritis (fig 6 *A*). These changes were always confined to an area close to the cardia, with 1 exception, in which the varices were localized in the extreme end of the gastric fundus. No esophageal varices were present in this particular case. My observations have since been confirmed by Pape.<sup>5</sup>



Fig 8—Varices localized in the lower portion of the esophagus in a young woman with cirrhosis of the liver. The clinical differential diagnosis was between tuberculous peritonitis and cirrhosis. The patient died from insufficiency of the liver shortly afterward. *A*, right oblique view. The arrow indicates the area in which the normal folds end and the varices begin. *B*, left oblique view.

The large diameter of the esophagus is striking in many cases of varices. It is produced largely by protruding vascular structures, which by filling the lumen distend the esophageal walls. A picture similar to that of idiopathic dilatation of the esophagus may result (fig 5). There is, however, no obstruction at the cardia. The barium passes freely into the stomach, although the emptying time and particularly the "cleaning"

<sup>5</sup> Pape, R. Ueber Deformationen des Magenfundus bei Oesophagusvarizen. *Röntgenpraxis* 9: 809-813, 1937.

time of the esophagus may be markedly prolonged. The discovery of a wide esophagus in a young person, particularly if the dilatation is localized to the lower end, demands a search for varices.

#### INFLUENCE OF VARIOUS FACTORS ON DEMONSTRABILITY OF VARICES

1 *Gravity*—Varices are usually much smaller with the patient in the upright than in the horizontal position. Therefore, the examination should be performed with the patient in the horizontal position.

2 *Peristalsis*—Peristalsis (figs 10 and 11) not infrequently decreases the size of the dilated vessels. At times one sees even large



Fig 9—Varices in a localized area in the lower end of the esophagus. The patient had albuminuria, hematuria and ascites. There was questionable enlargement of the spleen, not confirmed by all examiners. A tentative clinical diagnosis was chronic nephritis and "old malaria spleen." The demonstration of varices proved the presence of obstruction in the portal system. Splenectomy showed the presence of thrombophlebitis of the splenic vein.

varices empty completely during contraction of the esophagus, and a normal relief may result locally. Therefore, the presence of normal mucosal folds during the phase of contraction does not prove the absence of varices. The influence of peristalsis on the size of the varices apparently varies from case to case but seems to be fairly characteristic for a given case.

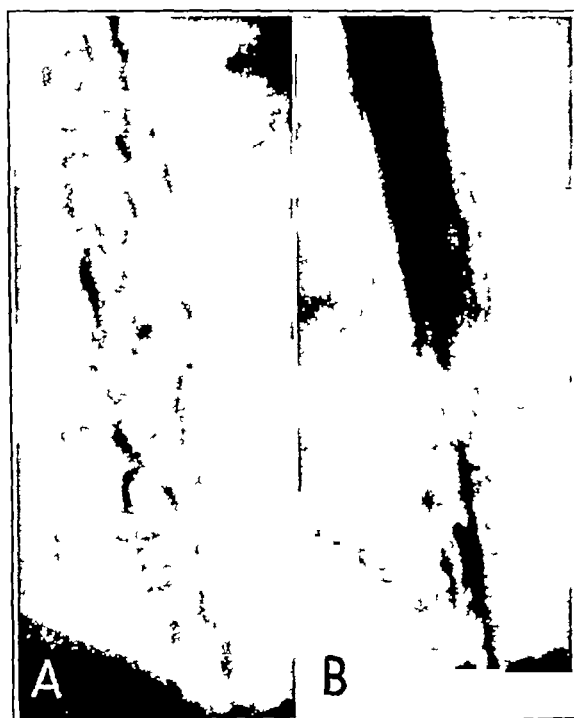


Fig 10—Changing size of varices during peristalsis in a patient with Banti's syndrome. The two pictures were taken within a few minutes of each other, with identical position of the patient. *A*, extensive varices during the resting phase of the esophagus. *B*, emptying of most varices during the contraction of the esophagus.



Fig 11—Decrease in size of the varicose veins during peristalsis in a patient with cirrhosis of the liver. *A*, phase of rest of the esophagus. *B*, phase of contraction.



3 *Projection*—If only one enlarged vessel is present, it may, like polarized light, undulate in one plane exclusively (fig 12). In such a case the characteristic sign of the vessel, namely its tortuosity, is absent if the examination is performed in the direction of this plane. On the other hand, the vessel becomes obvious if the roentgen rays are perpendicular to the plane in which the vessel swings. The plane of undulation varies from case to case and cannot be predicted. For this reason it is necessary to examine the esophagus routinely in several projections and to take films in at least two projections which are about



Fig 12—Influence of the projection on the demonstrability of a varicose vein. The tortuous vein undulates in one plane only. The vessel in this case is not visible in the right anterior oblique view (C), while it is clearly seen in the left anterior oblique view (A and B) and particularly well on the spot film in this projection (B).

90 degrees different from each other. As the phenomenon described is particularly common in the presence of small varices, such views are of special importance in those cases in which fluoroscopic examination reveals no abnormality.

4 *Respiration*—Quiet respiration does not noticeably influence the enlarged vessels, but deep inspiration and expiration at times change their size. They may be slightly smaller with inspiration and larger with expiration. These findings are by no means constant, since the

influence of the changing intrathoracic pressure during respiration is rather complicated. I have previously described<sup>4</sup> a test in which changes in intrathoracic pressure were used for demonstration of changes in the size of the varices. Marked differences in pressure were produced by employing the Valsalva test (expiratory effort with closed glottis after deep inspiration) and the Mueller test (inspiratory effort with closed glottis after deep expiration). At times an increase in the size of the vessels was observed following the Valsalva test, while at other times such an increase followed the Mueller test. The variable results are apparently due to the fact that the size of the vessels depends on two factors: (1) the increased pressure in the thorax and therewith in the esophagus, which tends to compress the vessels during the Valsalva test, and (2) the increased pressure which exists during the Valsalva test within the vascular system proximal to the anemic lungs, as a result of which the varices tend to be enlarged. This test is of some theoretic interest, but in practice it has not been of great help, partly owing to the fact that only a few patients show sufficient intelligence and cooperation for its performance. In the routine examination I believe it best to take films after slight inspiration, since during this phase the lower end of the esophagus is stretched slightly, thus obviating the possibility of misinterpreting tortuous folds in a slack esophagus.

#### DIFFERENTIAL DIAGNOSIS

In cases of extensive varicosities the roentgen appearance of the esophagus is usually so characteristic that differential diagnostic difficulties rarely arise. The situation is different when the varices are small and localized. Air bubbles in the esophagus may occasionally assume the shape of small varices, in which case reexamination prevents error.

Slightly tortuous folds, which occur not uncommonly in the lower part of the esophagus, especially in elderly persons, simulate small varices. The latter are usually slightly larger in caliber than the tortuous folds, and in addition the size of one dilated vessel usually contrasts with the narrower normal folds. Films taken during inspiration, which stretches the tortuous folds of the esophagus, may be of help in differential diagnosis. The misinterpretation of tortuous gastric folds in a small hiatus hernia of the stomach may be prevented by adequate filling of the esophagus and stomach with barium.

A more important problem is the differential diagnosis between varices and "curling" of the esophagus (figs 13 and 14). "Curling" is a peculiar phenomenon seen occasionally during deglutition, in which, during the contraction, multiple irregular toothlike projections are seen along the edges of the esophagus. If closely spaced they may produce a scalloped appearance of the organ. The phenomenon appears and disap-

pers rapidly, but it can usually be easily reproduced by letting the patient swallow again, with or without additional barium. I believe, with Fleischner,<sup>6</sup> that the picture is produced by multiple adhesions of the esophageal wall which prevent sufficient collapse of the organ during contraction. Clinical symptoms are apparently not present, nevertheless, the recognition of "curling" is important for reasons of differential diagnosis. Since the profile picture of varices may be similar to that of "curling," it is necessary to rely for diagnosis on the relief picture, which is distinctly different.

The most important diagnostic question from the clinical point of view is the differentiation between varices and cancer of the esophagus.



Fig 13—"Curling" of the esophagus, probably produced by multiple areas of adhesions. Note the definite point of adhesion at  $x$ .

The marked irregularity of the inner relief in cases of extensive varices produces a picture which occasionally closely simulates that of cancer (Pohlandt<sup>7</sup>).

Since for all practical purposes, if varices are present they are always immediately above the diaphragm, they must be differentiated from cancer in this region only. The exact roentgen study of the lesion in most cases readily outlines the cancer, with its sharp edges and its ulcer-

<sup>6</sup> Fleischner, F. Die Divertikel der Speiseröhre. Haft-oder Adhäsionsdivertikel, Fortschr. a. d. Geb. d. Röntgenstrahlen **45** 627-664, 1932.  
<sup>7</sup> Pohlandt, K. Oesophagusvarizen oder Carcinom? Röntgenpraxis **3** 889-895, 1931.

ation, in contrast to the nonulcerated, poorly defined defect produced by varices. Of great help is the study of the elasticity of the esophagus. The esophagus becomes rigid in most cases of cancer, but it never loses

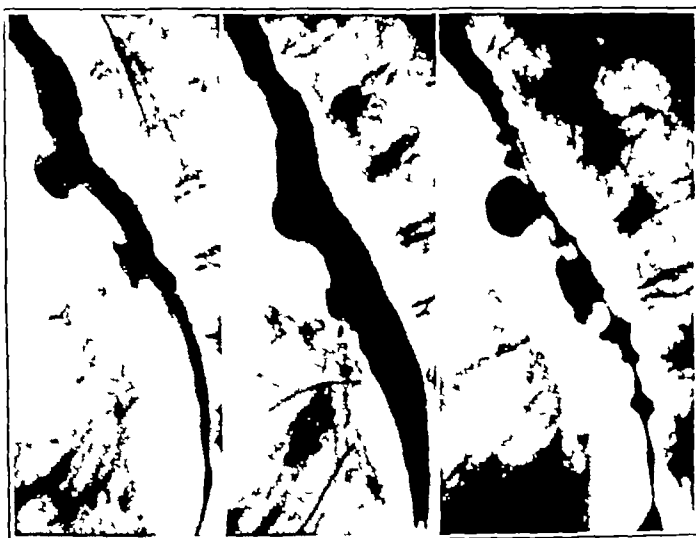


Fig 14—Adhesion diverticula, together with "curling"

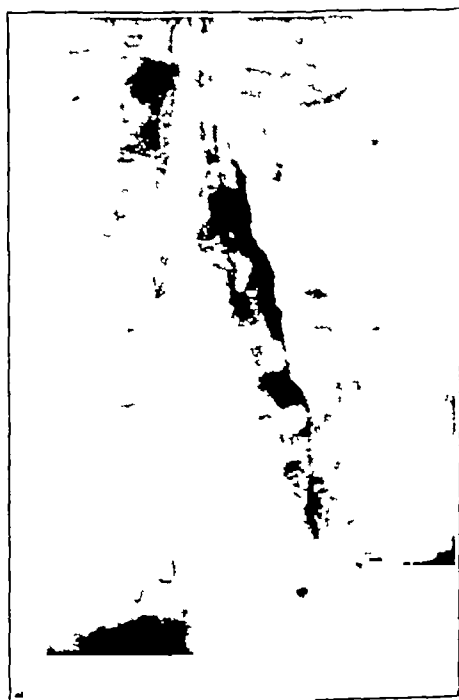


Fig 15—Extensive carcinoma of the esophagus, simulating varices. The patient had dysphagia, which was distinctly against the diagnosis of varices.

its elasticity with the most extensive varices. The organ can be easily widened by a large amount of barium, and it appears flexible during peristalsis and respiration and with the pulsation of the heart. The

varices produce no obstruction, though emptying of the esophagus may be markedly delayed by the pronounced irregularities of the inner surface. The disappearance of varices during peristalsis may occasionally be the deciding differential point. Usually, however, the localization, the appearance and the elasticity of the questionable area allow a ready differentiation between the two lesions. Should all these signs become unreliable in a rare case, a clinical symptom, namely, dysphagia, may be of decisive importance. Contrary to some reports in the literature (Oppenheimer<sup>2</sup>), I have never seen dysphagia in cases of the most extensive varices, even when the emptying time of the esophagus was markedly prolonged (more than two hours in 1 of these cases). Hence, difficulties in swallowing should not be explained on the basis of varices (fig 15).

#### CLINICAL IMPORTANCE OF ROENTGEN DEMONSTRATION OF VARICES

Congenital varices have been described in rare cases. A slight degree of telangiectasia, usually in the upper portion of the esophagus, has been found in elderly persons in whom there was no evidence of portal obstruction (Kaufmann<sup>8</sup>). Such cases are exceptions. For all practical purposes, the roentgen demonstration of varices in the lower end of the esophagus proves the presence of obstruction in the portal circulation. In all my cases in which postmortem examination was done, either cirrhosis of the liver or thrombosis of the splenic vein was found to account for the varicose collateral vessels. I have not observed a proved case in which pressure on the portal vein or its branches by tumor masses produced esophageal varices.

The clinical picture of cirrhosis of the liver may be classic, and then the demonstration of varices furnishes only confirmatory evidence. In other cases the diagnosis is suspected but becomes certain with the visualization of varices. Finally, there are those cases in which the diagnosis is not even entertained. In this connection, I have seen patients with esophageal varices in whom the liver and spleen were not palpable and in whom demonstrable ascites was absent, in other words, patients in whom the varices were the only demonstrable anatomic evidence of cirrhosis of the liver. The demonstration of varices has always proved helpful regardless of whether the diagnosis of cirrhosis was unsuspected, suspected or believed to be certain prior to roentgen examination. The first case to be reported may serve as an example.

<sup>8</sup> Kaufmann, E. *Pathology for Students and Practitioners*, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929.

## REPORT OF CASES

CASE 1—An Italian woman 44 years old entered the hospital because of swelling of the ankles and slight dyspnea on exertion. Physical examination showed a large abdomen with questionable free fluid. There was a tender epigastric mass in addition to a questionable mass in the left upper quadrant. The latter was not felt by all the examiners. Pelvic examination showed masses in both lateral vaults, which were tender to palpation. The clinical impression was that of malignant tumor arising in the pelvic organs, with metastases to the liver, lung and brain. Lymphoma was thought another possibility. Roentgen examination showed varices in the lower third of the esophagus and the probable presence of a small liver and an enlarged spleen. Hepatic damage was then confirmed by positive results from Takata-Ara and bromsulphalein tests (90 per cent retention in one hour). At discharge, the masses in the upper part of the abdomen were thought to be the liver and spleen. The patient returned to the hospital one year later, with a similar picture.

Not all patients with cirrhosis show varices roentgenologically. In a previous statistical analysis<sup>1</sup> I found that varices were demonstrable in about 50 per cent of all cases of cirrhosis and that the percentage was higher in cases of advanced involvement with associated splenomegaly, ascites or hematemesis.

Varices are even more frequently seen in patients who present the so-called Banti's syndrome. At the Massachusetts General Hospital, 15 patients were examined roentgenologically in the last six years in whose cases the final clinical diagnosis was Banti's syndrome. In 12 of these patients the presence of congestion within the portal system was confirmed by operation or autopsy. Of the 3 who came to autopsy, 2 had thrombosis of the splenic vein, and 1 had cirrhosis of the liver. In 3 of the 15 cases the diagnosis was based on clinical evidence only. Varices were observed roentgenologically in 13 of these patients. One of the 2 in whose cases roentgen study gave negative results was a young child. The clinical diagnosis was considered doubtful at discharge, and an operation was not performed. The other was a patient with repeated hematemesis. At operation markedly dilated veins were found on the outside of the stomach, together with slight enlargement of the spleen. It will be seen that, in my material, varices were demonstrable in nearly all cases of Banti's syndrome. The varices in this group are usually very extensive<sup>9</sup> (figs 3A, 6B and 10), small localized varicosities being less commonly seen (fig 9).

In my experience the demonstration of varices has proved to be of importance also in the diagnosis of primary carcinoma of the liver,

<sup>9</sup> Brdiczka, I. G., and Tschakert, J. Die roentgenologische Diagnostik der Oesophagusvarizen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **46** 156-166, 1932.  
 Plotz, M., and Reich, N. E. Esophageal Varices in Portal Hypertension (Pathogenesis and Diagnosis by Roentgenography), *Am. J. Digest. Dis.* **5** 357-360, 1938.  
 Greenwald, H. M., and Wasch, N. J. Roentgenological Demonstration of Varices as Diagnostic Aid in Chronic Thrombosis of Splenic Vein, *J. Pediat.* **14** 57-65, 1939.

owing to the fact that this disease is usually associated with cirrhosis of the liver (in 87 per cent of the cases from the Massachusetts General Hospital<sup>10</sup>) The demonstration of esophageal varices in a patient who is known to have malignant disease (e g, pulmonary metastasis) and who has a mass in the region of the liver is evidence highly suggestive of the presence of primary carcinoma of the liver

Visualization of varices offers much help in cases of hematemesis Establishment of the source of bleeding is important for diagnosis, prognosis and treatment Roentgen recognition of varices has decreased the number of cases of so-called roentgen-negative hematemesis Thereby, unnecessary exploratory laparotomies performed in a search for the bleeding point and prolonged medical dietary regimens for hypothetic bleeding ulcers have been avoided Furthermore, the prognostic importance of the demonstration of varicosities was impressive in a number of my cases in which the patients died of hemorrhage weeks or months after the examination In some of these cases the hemorrhage was the first and only one

The discovery of varices is valuable in differentiating the causes of ascites I have seen patients with ascites in whose cases the suspected clinical diagnosis was abdominal malignant tumor and others in whose cases the possibility of cardiac ascites was discussed, while 1 patient was thought to have tuberculous peritonitis In all these cases the demonstration of varices proved that the ascites was due to portal obstruction, i e, cirrhosis of the liver

The diagnostic importance of the demonstration of varices in patients with splenomegaly cannot be overemphasized I have had several cases in which visualization of esophageal varices was the decisive diagnostic step whereby lymphoblastoma, etc, as a cause of the splenomegaly was excluded The following case will serve as an example

CASE 2.—A man 58 years old complained of anorexia and loss of weight for six months The liver was found to be enlarged There was a mass in the left upper quadrant of the abdomen, the nature of which was debated The house staff favored a diagnosis of malignant tumor, and one of the visiting physicians diagnosed cirrhosis of the liver, while two others made the presumptive diagnosis of lymphoma Lymphoma was considered to be a definite possibility even after roentgen demonstration of varices had been carried out Roentgen ray treatment as a therapeutic test was advised and started As there was still much clinical debate about the nature of the mass, a laparotomy was finally decided on It confirmed the roentgen diagnosis of cirrhosis This case goes back a number of years to a time at which roentgen diagnosis of varices and its consequences were not fully appreciated At present the radiation test and an exploratory laparotomy in such a case would be considered unnecessary and even contraindicated

<sup>10</sup> Schatzki, R. Roentgenological Diagnosis of Primary Carcinoma of the Liver, to be published

Finally, I have in a few cases found the demonstration of varices helpful in the differential diagnosis of a mass in the left upper quadrant of the abdomen. In such a case, if varices are present, the mass in all probability represents an enlarged spleen.

CASE 3—A man 52 years old, with a history of rectal bleeding for four years, showed a palpable mass in the upper part of the abdomen. He was given a barium sulfate enema, and a roentgen study of the upper part of the gastrointestinal tract was made to establish the location of the supposed intestinal tumor. Roentgen examination showed the mass to be outside the gastrointestinal tract and to represent an enlarged, lobulated spleen. The presence of extensive esophageal varices established the existence of portal obstruction (fig. 2).

Roentgen demonstration of varices is no longer a rare curiosity but is an important part of the daily routine examination of the gastrointestinal tract.

#### SUMMARY

The roentgen diagnosis of esophageal varices is discussed, based on examination in 116 cases of varices.

The technic of demonstrating varices and their roentgen appearance are described.

Stress is laid on the visualization of small localized varices, for which a combination of fluoroscopic and roentgenographic methods is essential.

Factors influencing the demonstrability of varices are the degree of filling of the esophagus, gravity, peristalsis, projection and respiration.

Unless these factors are considered, a normal appearance of the esophagus may result even in cases of extensive varicosities.

Differentiation between varices and air bubbles, tortuous normal folds, small hiatus hernia, "curling" and cancer is discussed.

The demonstration of varices is of clinical importance in the diagnosis of cirrhosis of the liver, of Banti's syndrome and of primary carcinoma of the liver. It is of great help in the differential diagnosis of hematemesis, acites and splenomegaly.



# BLEEDING ESOPHAGEAL VARICES

AN EVALUATION OF METHODS DIRECTED TOWARD THEIR  
CONTROL, ESPECIALLY BY DIRECT INJECTION  
OF A SCLEROSING SOLUTION

WALTMAN WALTERS, M D

HERMAN J MOERSCH, M D

AND

D ANGUS MCKINNON, M D

Fellow in Surgery, the Mayo Foundation  
ROCHESTER, MINN

Esophageal varices develop as a result of obstruction of the portal or splenic veins because the esophageal veins are one of the three sites of communication between the portal and caval systems. Since the veins in the submucosa of the lower part of the esophagus are poorly supported by loose connective tissue, with the increase in the quantity of blood passing through them varices develop, become superficial to esophageal mucosa and are prone to rupture.

The frequency with which bleeding occurs from esophageal varices was emphasized by Preble's<sup>1</sup> review of 60 cases of fatal gastrointestinal bleeding in 80 per cent of which esophageal varices were found. In 50 per cent of the cases in which varices were present, macroscopic demonstration of the site of perforation of the varix was possible. Rivers and Wilbur found that in 5 per cent of a group of 668 patients with a history of hematemesis bleeding was attributable to cirrhosis of the liver or to splenic anemia.

Methods directed toward prevention of fatal bleeding have consisted of (1) splenectomy to reduce the blood entering the portal vein, (2) omentopexy to establish collateral circulation around the liver through the veins of the peritoneum and the abdominal wall, especially through the superior epigastric veins, (3) interruption of the blood flow through the esophageal veins by ligation of the coronary vein, with or without

From the Division of Surgery (Dr Walters) and the Division of Medicine (Dr Moersch), the Mayo Clinic

1 Preble, R. B. Conclusions Based on Sixty Cases of Fatal Gastro-Intestinal Hemorrhage Due to Cirrhosis of the Liver, *Am J M Sc* **119** 263-280 (March) 1900

2. Rivers, A. B., and Wilbur, D. L. The Diagnostic Significance of Hematemesis, *J A M A* **98** 1629-1631 (May 7) 1932

splenectomy and, more recently, (4) injection of a sclerosing solution transperitoneally into the paraesophageal veins and directly into the varices through the esophagus

#### ETIOLOGY

The factor underlying the development of esophageal varices is not always clear. While Banti's disease and splenic anemia are the conditions most frequently associated with the development of esophageal varices, they cannot, as Dock and Warthin<sup>3</sup> have pointed out, be regarded as distinct clinical entities but may occur as a result of obstruction of the portal or the splenic vein. Many hypotheses have been advanced to account for obstruction of the portal or the splenic vein, but they will not be discussed in this presentation. The physiologic changes involved in the development of esophageal varices have been well demonstrated in the anatomic studies of McIndoe<sup>4</sup> and of Kegaries<sup>5</sup> (fig 1). Obstruction of the veins may be produced by either intrinsic or extrinsic factors. With the development of obstruction of the portal or of the splenic vein, there is an attempt on the part of nature to establish an anastomosis by means of which the blood from the portal vein can return to the general systemic circulation. This, as a rule, will take place through channels of communication that already exist. The route to be selected is somewhat dependent on the site of the obstruction in the splenic or portal vein. According to McIndoe,<sup>4</sup> the communication that will be established usually takes place through one of three sites (fig 2)

1 At the point of transition between absorbing and protective epithelium. (a) Between the coronary vein of the stomach and the intercostal, azygos and diaphragmatic veins. (b) Between the superior hemorrhoidal and the middle and inferior hemorrhoidal veins.

2 At the site of embryologic circulation—the falciform ligament containing the paraumbilical veins.

3 At all situations within the abdomen where the gastrointestinal tract, its appendages or glands developed from it become retroperitoneal developmentally or adherent to the abdominal wall pathologically.

The communications that occur between the coronary vein of the stomach and the azygos, intercostal and diaphragmatic veins are of

3 Dock, G, and Warthin, A. S. A Clinical and Pathological Study of Two Cases of Splenic Anaemia, with Early and Late Stages of Cirrhosis, *Am J M Sc* **127** 24-55 (Jan) 1904.

4 McIndoe, A. H. Vascular Lesions of Portal Cirrhosis, *Arch Path* **5** 23-42 (Jan) 1928.

5 Kegaries, D. L. (a) The Venous Plexus of the Oesophagus, *Surg, Gynec & Obst* **58** 46-51 (Jan) 1934, (b) The Venous Plexus of the Esophagus Its Pathologic and Clinical Significance, *Proc Staff Meet, Mayo Clin* **8** 160-163 (March 15) 1933. Walters, W., in discussion on Kegaries.

the greatest importance, for they are primarily concerned in the development of esophageal varices. McIndoe has pointed out that in the presence of obstruction of the portal vein these communications are most likely to develop, as they are the most direct and the shortest route between the portal and the general systemic circulation. Furthermore, in the presence of obstruction of the portal vein the pressure within the portal circulation is increased, and in the absence of valves the flow of blood through the coronary vein is undoubtedly reversed and thus readily exerts pressure on the esophageal plexus. Kegaries<sup>5b</sup> has clearly demon-

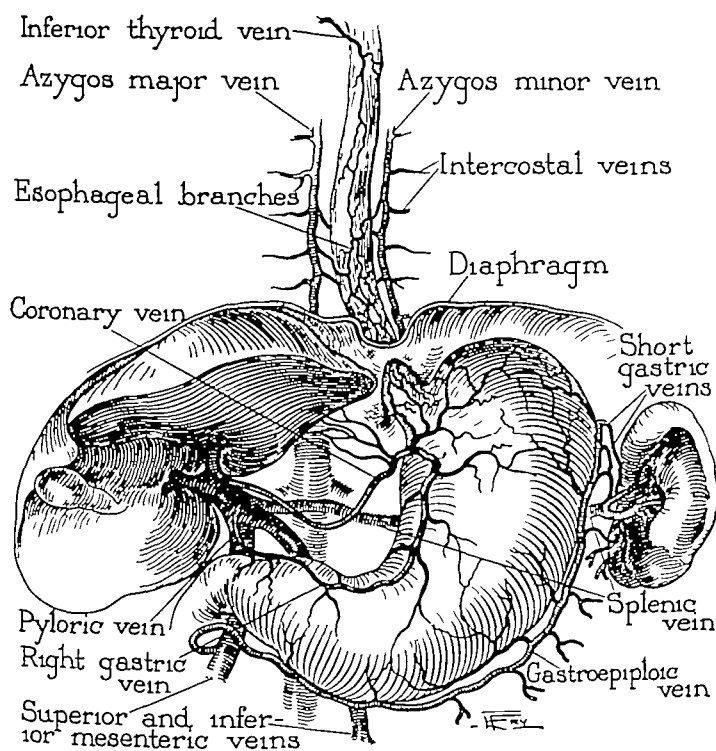


Fig 1—Relation of the coronary vein of the stomach to the esophageal veins (From Kegaries, D L. *The Venous Plexus of the Oesophagus*, Surg, Gynec & Obst. 58 46-51 [Jan] 1934)

strated the manner in which the anastomosis takes place between the portal and the caval circulation through the splenic veins in the gastro-ligament by way of the cardia and the lower part of the esophagus. The coronary vein of the stomach branches as it pierces the muscular coats to reach the submucosa of the cardia. In this region the branches of the coronary vein break up into a number of small longitudinal venules which have no cross communication for a distance of approximately 3 or 4 cm. At this point they break up into a rich plexus, which anastomoses freely with branches of the splenic vein entering the stomach.

through the short gastric veins. The larger trunks are extremely tortuous and run in a longitudinal direction. This plexus of veins communicates by perforating branches with larger periesophageal trunks, which likewise run in a longitudinal direction and usually number three or four. The latter trunks communicate with the azygos, the intercostal and the diaphragmatic veins of the systemic circulation (fig 3)

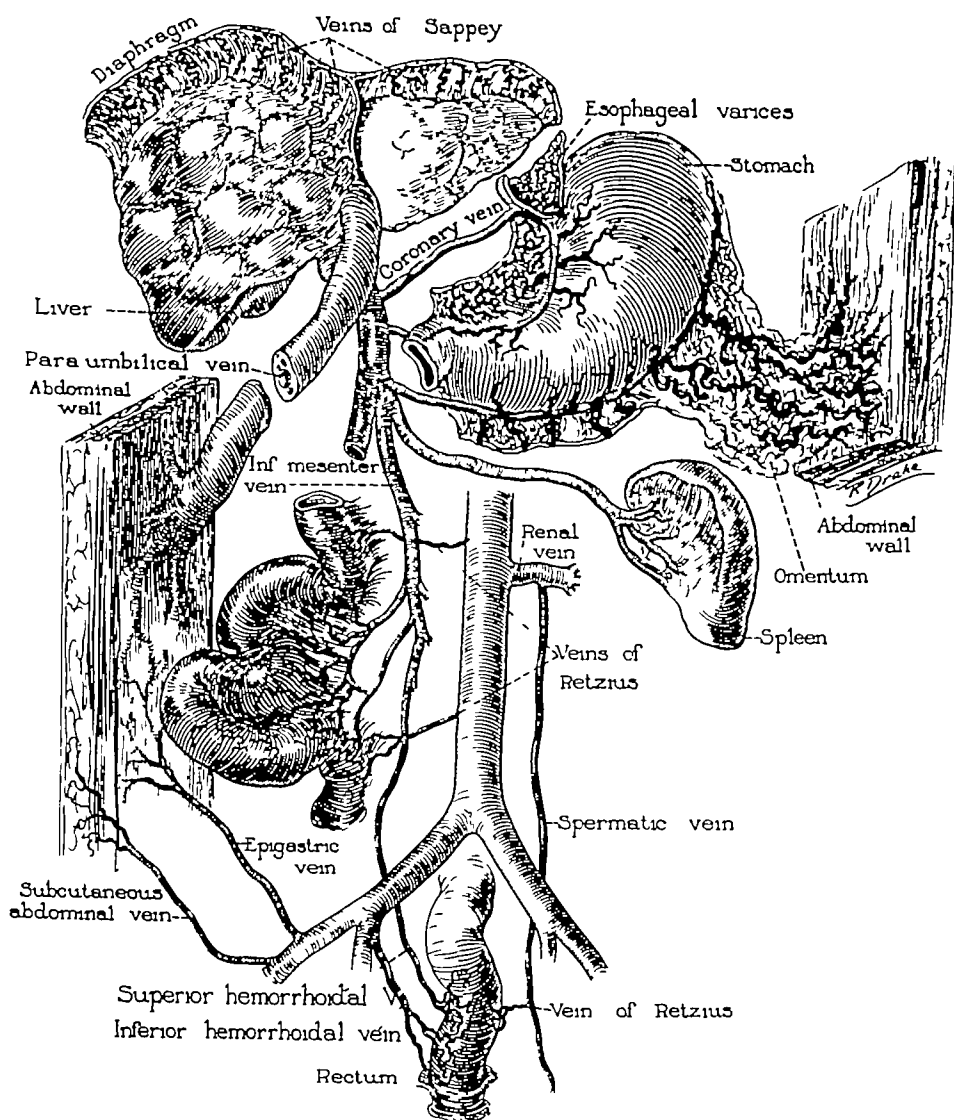


Fig 2—The most likely source of communication between the portal and the systemic circulation (From McIndoe, A H Vascular Lesions of Portal Cirrhosis, Arch Path 5 23-42 [Jan] 1928)

The veins in the submucosa of the lower part of the esophagus are poorly supported by loose connective tissue. Because of their situation they are constantly exposed to trauma and consequently most prone to lead to fatal bleeding. In addition, there is the effect of the changing suction which takes place in the thoracic cage with respiration. Eso-

phageal varices may involve the greater part of the esophagus but usually are limited to the lower half

# DIAGNOSIS

One of the greatest obstacles to the development of procedures for the treatment of esophageal varices has been inability to make an early



Fig 3—Filling of esophageal venules following injection through the coronary vein (From Kegaries, D L The Venous Plexus of the Oesophagus, Surg, Gynec & Obst 58 46-51 [Jan] 1934)

diagnosis In 1925, Jackson and his associates<sup>6</sup> called attention to the possible value of esophagoscopy study as an aid in the diagnosis of

<sup>6</sup> Jackson, C, Tucker, G, Clerf, L H, Lukens, R M and Moore, W F Hematemesis A Plea for Objective Methods of Diagnosis, J A M A 85 870 875 (Sept 19) 1925

esophageal varices The procedure did not come into general use, however, because of the fear of producing fatal hemorrhage It was not until 1928 that Wolf<sup>7</sup> first described the roentgen technic for diagnosis of esophageal varices Kirklin and one of us (Moersch),<sup>8</sup> in 1931, called attention to the value of combining roentgenoscopic and esophagoscopic examination as a diagnostic measure and pointed out that it might also be of value in following the developments subsequent to treatment With proper care, however, esophagoscopic procedures can be carried out with a minimum of risk

#### NONSURGICAL TREATMENT

In addition to the surgical procedures to be described, many other methods have been advocated for the prevention and control of bleeding from esophageal varices Measures which have been employed are dietary restrictions, the use of local applications to the varix (diathermy, local compression and so forth), injection of solutions into the general circulation to stimulate coagulation and venesection, as suggested by Drenckhahn,<sup>9</sup> to decrease the viscosity of the blood Most of these procedures, however, are merely palliative and therefore of only temporary value

#### SURGICAL PROCEDURES

"The spleen is an organ of contradiction and mystery, in health, of relatively unimportant function, in disease, a menace of grave import" (Mayo<sup>10</sup>)

*Splenectomy*—The surgical procedure that has been employed most frequently is splenectomy In discussing the surgical treatment of the spleen, Mayo,<sup>11</sup> in 1912, advised splenectomy in cases of splenic anemia on the theoretic ground that the enlarged spleen contributes to the reduction in "the number and value of the red blood corpuscles and low hemoglobin" Although this paper was read before the Clinical Congress of Surgeons of North America on Nov 11, 1912, it was not published until 1913 He reported at that time that of the 27 splenectomies performed at the Mayo Clinic from April 6, 1904, to Oct 21, 1912, 18 were for splenic anemia (5 patients had Banti's syndrome) There were 2

<sup>7</sup> Wolf, G Die Erkennung von Ösophagus-Varizen im Röntgenbilde, Fortschr a d Geb d Röntgenstrahlen **37** 890-893, 1928

<sup>8</sup> Kirklin, B R, and Moersch, H J Report of a Case of Roentgenologically Demonstrable Esophageal Varices Complicating Splenomegaly, Radiology **17** 573-575 (Sept) 1931

<sup>9</sup> Drenckhahn, C H A New Approach to the Prevention of Hemorrhages from Esophageal Varices as Occur in Cirrhosis and Banti's Disease, Am J Digest Dis **6** 462-465 (Sept) 1939

<sup>10</sup> Mayo, W J The Enlarged Spleen, South M J **21** 13-16 (Jan) 1928

<sup>11</sup> Mayo, W J Surgery of the Spleen, Surg, Gynec & Obst **16** 233-239 (March) 1913

operative deaths in the 27 cases, both in cases of splenic anemia. The pathologic observations in the cases of splenic anemia showed chronic diffuse splenitis in 13 cases, endothelial proliferation (Gaucher's type) in 3 and lymphoid hyperplasia in 2 (lymphosarcoma in 1 and lymphoma [?] in 1). Twelve of the patients who had suffered from splenic anemia had been well for from one to seven years after operation. In 1929, Mayo<sup>12</sup> postulated that cirrhosis of the liver in cases of Banti's disease probably results from the toxic material gathered in the spleen and sent to the liver, which the liver, failing to detoxicate, attempts to encapsulate diffusely, with the introduction of general fibrosis. With the dysfunction of the enlarged spleen its already large blood supply greatly increases, and, since it is joined with the portal vein, it is estimated that the blood from the spleen supplies 20 per cent of the blood in the portal circulation. This is greatly increased with the increase in the size of the spleen, for the splenic vein and its branches are greatly increased in size. With removal of the spleen and ligation of the splenic vein this supply of blood to the portal vein would cease.

It was also assumed as a possibility that after the removal of the enlarged spleen in cases of splenic anemia the denuded parietal peritoneum of the posterior portion of the abdominal cavity, which had been in contact with the spleen, might be the site of formation of a network of collateral veins through which circulation between the portal system and the inferior vena cava could occur. In 1933, Kegaries<sup>13</sup> showed that ligation of the branches of the splenic vein going to the cardia and the esophagus through the short gastric veins decreased the flow of blood through the esophageal veins when the spleen was removed and suggested that this is one of the important benefits of splenectomy. Splenectomy, however, did not completely solve the problem, for Mayo<sup>12</sup> in 1929, in his report of 148 cases of splenectomy for splenic anemia (with 14 deaths), stated that in about 10 per cent of the cases in which recovery took place after splenectomy the patients died at some time in the next ten years of hemorrhages from the stomach, probably from ruptured varices in the lower end of the esophagus. In 1931, Pemberton<sup>13</sup> reported the recurrence of hemorrhage from esophageal varices after splenectomy in approximately 50 per cent of 98 cases.

In a recent review of the results of various surgical procedures performed at the Mayo Clinic on patients with histories of bleeding esophageal varices, Giffin and two of us (Walters and McKinnon)<sup>14</sup> found

12 Mayo, W. J. The Enlarged Spleen, *California & West Med* 30:382-386 (June) 1929.

13 Pemberton, J. deJ. Results of Splenectomy in Splenic Anaemia, Haemolytic Jaundice, and Haemorrhagic Purpura, *Ann Surg* 94:755-765 (Oct.) 1931.

14 Giffin, H. S., Walters, W., and McKinnon, D. A. Unpublished data.

that 41 of 103 splenectomized patients had had no subsequent hemorrhages for periods varying from a few months to more than fifteen years after operation (table 1). It is to be noted that 80 of the patients underwent splenectomy alone, 12 underwent splenectomy and ligation of the coronary vein, with or without omentopexy, and 11 underwent omentopexy, but not ligation of the coronary vein, with the splenectomy.

From Jan 1, 1908, to Dec 31, 1934, inclusive, splenectomy was performed for splenic anemia in 180 cases at the Mayo Clinic. One

TABLE 1—*Effect of Different Surgical Procedures on Bleeding Esophageal Varices in Cases of Splenic Anemia*

Procedure	Number of Cases	Bled Preoperatively	Bled Postoperatively	Untraced	Hospital Deaths	No Subsequent Hemorrhage
Splenectomy alone	80	80	33	5	9	33
Splenectomy, ligation of coronary vein and omentopexy	3	3	2	0	0	1
Splenectomy and ligation of coronary vein	9	9	6	1	0	2
Splenectomy and omentopexy						
Preoperative bleeding	5	5	1	1	2	1
No preoperative bleeding	6	0	1	1	0	4

TABLE 2—*Survival After Operation for Patients with Splenic Anemia Undergoing Splenectomy and Associated Surgical Procedures*

Five Year Survival After Operation *			Ten Year Survival After Operation *			Fifteen Year Survival After Operation *		
Total Patients	Traced Patients	Percent age of Survival	Total Patients	Traced Patients	Percent age of Survival	Total Patients	Traced Patients	Percent age of Survival
180	170	56.5	150	135	41.5	102	89	29.2

\* The five year group comprises the patients on whom operation was performed five or more years prior to the time of inquiry, that is, on Dec 31, 1934, or earlier; the ten year group comprises those on whom operation was performed on Dec 31, 1929, or earlier; the fifteen year group comprises those on whom operation was performed on Dec 31, 1924, or earlier.

hundred and seventy patients were traced, of whom 56.5 per cent lived for five years or more after operation. Of 150 patients on whom operation had been performed ten years or more before the time of inquiry, 135 were traced, of these, 41.5 per cent were living at the end of ten years, while 29.2 per cent lived for fifteen years or more after operation (table 2). When these results are compared with those in the operative cases in which the survival rate was based on the onset of symptoms (table 3) it is found that approximately 73 per cent lived five years or more, 56 per cent, ten years or more, and 52 per cent,



fifteen years or more. There was a hospital mortality rate in the 180 cases of 10 per cent. The causes of death (operative mortality) are shown in table 4.

*Ligation of the Coronary Vein*—In 1929, Rowntree, McIndoe and one of us (Walters),<sup>12</sup> on the basis of anatomic studies of the portal circulation, advocated ligation of the coronary vein as a possible means of preventing bleeding from esophageal varices. The operation was

TABLE 3—*Survival After Onset of Symptoms for Patients with Splenic Anemia Undergoing Splenectomy and Associated Surgical Procedures*

Five Year Survival After Onset of Symptoms *			Ten Year Survival After Onset of Symptoms *			Fifteen Year Survival After Onset of Symptoms *		
Total Patients	Traced Patients	Percent age of Survival	Total Patients	Traced Patients	Percent age of Survival	Total Patients	Traced Patients	Percent age of Survival
180	177	72.9	167	158	50.3	115	103	52.4

\* The five year group comprises the patients whose symptoms began five or more years prior to the time of the inquiry, that is on Dec 31, 1934, or earlier; the ten year group comprises those whose symptoms began on Dec 31, 1929, or earlier; the fifteen year group comprises those whose symptoms began on Dec 31, 1924, or earlier.

TABLE 4—*Causes of Death*

	Hospital Deaths
Mesenteric thrombosis (1 also bled from varices)	2
Pulmonary complications (2 pneumonia, 1 influenza, 1 pulmonary edema and 1 septic pleurisy)	5
Postoperative hemorrhage	3
Pulmonary emboli	2
Subdiaphragmatic and subhepatic abscesses	1
Hepatic insufficiency	1
Suicide, also had portal emboli	1
Eighteen deaths in 180 cases hospital mortality 10 per cent	

performed in 10 cases (table 5). Most of these were cases of cirrhosis of the liver.

Of the patients in these cases, 1 was operated on in 1929 and died in March 1932, having had repeated gastric hemorrhages. Of the 3 patients operated on in 1931, 2 were followed. One reported in 1935 that he had had two subsequent hemorrhages, the other died of cerebral hemorrhage two years after operation. Two patients operated on in 1933 died

15 Rowntree, L. G., Walters, W., and McIndoe, A. H. End Result of Tying of the Coronary Vein for Prevention of Hemorrhage from Esophageal Varices, Proc Staff Meet, Mayo Clin 4 263-264 (Sept 4) 1929. Walters, W., Rowntree, L. G., and McIndoe, A. H. Ligation of the Coronary Veins for Bleeding Esophageal Varices, *ibid* 4 146-147 (May 8) 1929.

of hepatic insufficiency In the case of 1 there was a question of hemorrhage In 1 of the 3 patients operated on in 1934, hepatic insufficiency with jaundice, ascites and edema developed in 1936 The second patient died in 1937 of hepatic insufficiency This patient had had repeated gastrointestinal hemorrhages

As was previously mentioned, ligation of the coronary vein and splenectomy were done in 9 cases (table 1) Those in which ligation of the coronary vein alone was done (4 cases) were cases of primary cirrhosis of the liver in which esophageal varices developed and in which hepatic insufficiency developed later and in most cases became the cause of death Hence the true merits of this operation in the treatment of bleeding esophageal varices associated with splenic anemia cannot be definitely determined at this time, since ligation of the coronary vein

TABLE 5—*Effect of Surgical Procedures on Bleeding Esophageal Varices in Patients with Cirrhosis of the Liver\**

Procedure	Number of Cases	Bled Preoperatively	Bled Postoperatively	Untraced	Died Subsequently	No Subsequent Hemorrhage
Ligation of coronary vein alone	4	4	2**	1	1, immediately 1, 2 years later	0
Ligation of coronary vein and omentopexy	6	4	2**	3†	6, all but one died within 3 years	1

\* One patient had syphilitic hepatitis

\*\* These patients have subsequently died, but we knew from follow ups that they had bled before death

† These patients are known to be dead, but their symptoms before death are unknown

alone has been done on too few patients to justify any decision about its value

*Omentopexy*—Since many observers have noted from time to time that nature, in her desire to divert blood back into the general circulation around a cirrhotic liver, attaches the omentum to the abdominal wall, it was suggested by Talma and his associates<sup>16</sup> that an attempt be made to assist in the establishment of such a method of collateral circulation by placing the omentum in contact with the branches of the veins of the abdominal wall, particularly the superior epigastric vein and its branches This could be done by scarifying the parietal peritoneum and suturing the omentum to it or by a modification which Mayo<sup>17</sup> described

16 Talma, Safe, Drummond, David, Morison and Rutherford, cited by Vander Veer, E A Talma Operation for Cirrhosis of the Liver, with Report of Cases, Surg, Gynec & Obst 15 278-281 (Sept) 1912

17 Mayo, W J The Surgical Treatment of the Cirrheses of the Liver and Their Complications, in Collected Papers of the Mayo Clinic, Philadelphia, W B Saunders Company, 1918, vol 10, pp 143-145

in 1918 and which at that time he had used in 28 cases, namely, drawing the omentum up through the peritoneal incision and into the incised rectus muscle, suturing it in that position and closing the fascia carefully over it. In discussing the merits of this procedure he stated, "On several occasions we have gone down a second time in the vicinity of the previous operation, with a view of increasing the omental attachments, and have found such extensive compensatory circulation, almost entirely venous, that we were obliged to desist, and even with difficulty controlled the hemorrhage." In 1933, Pemberton,<sup>18</sup> in discussing the value of omentopexy as an adjunct to splenectomy performed on patients with splenic anemia, stated that he had used it in 15 cases, in which subsequent bleeding had not occurred. This must be qualified by a statement that he had not been in touch with some of the patients for a considerable period. In 1 of Pemberton's cases the sequence of events that followed omentopexy is worthy of description.

The patient in this case, who had Banti's disease, had complained bitterly of pain in the right side, and the clinician had suspected that the gallbladder or the appendix was the cause of this. It was felt, therefore, that it was advisable to explore the gallbladder and the appendix before performing splenectomy. At operation it was found that there was ascites grade 2 (on a basis of 1 to 4). This patient, according to the bromsulphalein test of hepatic function before operation, had had dye retention, grade 2, and at operation a biopsy specimen of the liver was taken, which showed portal cirrhosis, grade 1, and fatty liver, grade 1 plus. As the appendix and the gallbladder were not grossly diseased, the wound was closed after omentopexy had been performed. The patient's convalescence was uneventful, three weeks later the hepatic function test showed no dye retention, and she was allowed to go home. On her return to the clinic, six weeks after omentopexy, the hepatic function test again showed no dye retention. Splenectomy was done, and no free fluid was found in the abdomen. The under surface of the anterior abdominal wall, where the omentopexy had been previously done, was inspected, and the omentum running into the abdominal wall seemed to be particularly richly supplied with blood vessels. The patient went through the operation nicely and had a normal convalescence.

Likewise in 1933, Pemberton<sup>18</sup> suggested that if recurrent bleeding from esophageal varices occurred in patients on whom he had done omentopexy it would be a good idea to inject a sclerosing solution directly into the esophageal varices through the esophagoscope. In the performance of omentopexy Pemberton<sup>18</sup> expressed a preference for incorporating the omentum in the abdominal wall, lateral to the incision

<sup>18</sup> Pemberton, J. deJ. Personal communication to the authors.

for laparotomy, so as not to jeopardize healing from this incision. In describing his technic he stated<sup>13</sup>

After separation of the several layers of the abdominal wall for 3 centimetres from the edge of the wound, a small incision is made through the peritoneum and posterior sheath of the rectus abdominis muscle, and a segment of omentum 14 to 20 centimetres is then drawn up through this opening and sutured. Similar incisions are made in the muscle and anterior sheath of the rectus abdominis, at successive levels, each lower than the preceding one, 2.5 centimetres or more apart, and the omentum is drawn through these, the distal 5 to 8 centimetres is then buried beneath the skin.

By bringing the omentum out in a steplike manner, conditions are established for the formation of new blood channels in each layer of the abdominal wall, and on account of the oblique course of the openings, the chances of troublesome herniation are minimized.

*Injection of Sclerosing Solutions into the Esophageal Varices*—In 1933, one of us (Walters), in discussing Kegaries' paper,<sup>5b</sup> suggested that it might be advisable to inject a sclerosing solution into the varices around the esophagus at the time of ligation of the coronary vein. This procedure has recently been carried out by Grace<sup>19</sup>. At about this time, Pemberton and one of us (Moersch<sup>20</sup>) became interested in the possibility of injecting a sclerosing solution into the veins directly through an esophagoscope. Before attempting to carry out the procedure on human beings, the experimenters thought it would be advisable to perform it on experimental animals. An attempt was made to produce varices of the esophagus in dogs. While they could produce enlarged vessels over the thoracic wall of the animal, they were unable to produce enlargement of the veins in the esophagus. Consequently, the idea of employing the method on human beings remained in abeyance. During 1939, Crafoord and Frenckner,<sup>21</sup> of Stockholm, reported that they had carried out this form of therapy successfully on a human being and that the patient had remained free from symptoms for approximately three years after treatment. Their report encouraged one of us (Moersch<sup>22</sup>) to attempt to duplicate the procedure. The successful result obtained by this method was reported by him at a meeting of the American Association for Thoracic Surgery, and an abstract of the case follows (case 1).

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<sup>19</sup> Grace, E., in discussion on Moersch<sup>22</sup>

<sup>20</sup> Moersch, H. J. Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. **15** 177-179 (March 20) 1940.

<sup>21</sup> Crafoord, C., and Frenckner, P. New Surgical Treatment of Varicose Veins of the Oesophagus, Acta oto-laryng. **27** 422-429, 1939.

<sup>22</sup> Moersch, H. J. The Treatment of Esophageal Varices by Injection of a Sclerosing Solution, read at the Meeting of the American Association for Thoracic Surgery, Cleveland, June 6-8, 1940.

CASE 1—A man 30 years of age came to the Mayo Clinic in February 1940 with a history of recurrent gastrointestinal hemorrhage. A diagnosis of Banti's disease or cirrhosis of the liver had been made elsewhere. The patient apparently had enjoyed the best of health until 1928, in which year he was suddenly stricken with a severe attack of hematemesis. He was hospitalized, and repeated transfusions of blood were necessary. The patient recovered from this attack satisfactorily and remained well for approximately one year, at the end of which he suffered a similar attack and transfusions of blood again were required. At this time enlargement of the spleen was noted and splenectomy was advised. At operation the spleen, which was approximately nine times the normal size, was removed. There is no record of the exact character of the spleen. After operation the patient did not experience recurrence of bleeding until 1936, in which year he again began to suffer from hemorrhage. Since that time he had been having recurrent attacks of bleeding which occurred with increasing frequency, and during the year prior to his coming to the clinic he had had four attacks, the last one occurring in December 1939.

On physical examination nothing of unusual consequence was found. The significant observations at laboratory investigation were as follows: There was a reduction in the value for hemoglobin to 9.6 Gm per hundred cubic centimeters,

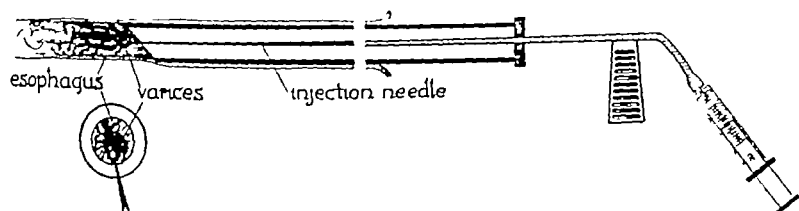


Fig 4—Instrument and needle employed in the injection of sclerosing solutions into esophageal varices. (From Moersch, H. J. The Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. 15: 177-179 (March 20) 1940)

and the blood smear was reported as showing macrocytic hypochromic anemia of the type associated with cirrhosis of the liver. Roentgen examination of the esophagus revealed esophageal varices involving the lower third of the gullet. It is rather interesting that the test for hepatic function did not show retention of dye.

A clinical diagnosis of cirrhosis of the liver with associated esophageal varices was made. One of us (Walters), who saw the patient in surgical consultation, suggested that this might be a suitable case in which to attempt control of the bleeding by injection of a sclerosing solution into the varices. In spite of the risk involved, the patient was rather anxious to have us attempt the procedure, because he lived in constant fear of a fatal hemorrhage.

Esophagoscopy was made with local anesthesia, and markedly enlarged varices involving the lower third of the esophagus were readily found. They were of such size that they almost completely obstructed the lumen of the gullet. They formed large, bluish nodular prominences which were soft and compressible. A suitable vein was selected for injection, and with a 25 caliber needle (fig 4) 0.5 cc of a solution of 2.5 per cent sodium morrhuate was injected. Much to the surprise of one of us (Moersch), the procedure was accomplished with practically no bleeding. Injections were given three more times at four day intervals, 1 cc of the solution being injected on each of these occasions.

The change that took place after the injection treatment was striking. The vessels into which the sclerosing solution had been injected lost their bluish color and became yellowish gray, they were firmer and smaller, and the surrounding mucous membrane became less congested. After the last injection the lumen of the esophagus, which had been almost completely obstructed by the enlarged varices, returned almost to its normal caliber, and it was possible to look into the stomach without difficulty.

In a recent communication received from the patient, he stated that he has had no further bleeding since his treatment, that the value for hemoglobin has increased to 81.9 per cent and that he has been feeling better than he has for several years.

Sufficient time has not elapsed in which to determine the efficacy of the injection treatment of esophageal varices, and it may be found necessary to repeat the procedure if further bleeding should take place. It is still uncertain whether the injection should precede or follow splenectomy and ligation of the coronary vein. At present one of us (Moersch) is inclined to believe that it would be advisable to carry out the splenectomy before the injection is attempted. It seems, however, that this procedure is worthy of serious consideration, as it offers a possible method of controlling bleeding that has not responded to any other form of therapy and thus may be successful in prolonging the life of the patient.

Since this report, one of us (Moersch) has carried out or attempted injection treatment of esophageal varices in 5 additional cases.

CASE 2—The patient was a man aged 40 years who had syphilitic hepatitis. He had been having gastric hemorrhages. Roentgen examination was reported as showing varices involving the lower half of the esophagus. The spleen was found to be enlarged, as was the liver. On esophagoscopy examination the varices were found to involve the lower part of the esophagus. Although they were numerous, they were very small in caliber, and Moersch had a great deal of difficulty in trying to insert the needle into the veins. Because of this, he did not feel that further injection was advisable at this time.

CASE 3—The patient was a woman 52 years of age. In October 1939 she had her first massive gastrointestinal hemorrhage. She had no further trouble until eight days before admission to the clinic, on June 8, 1940. She stated that cholecystectomy had been performed seven years previously. On physical examination the spleen was not palpable. The patient was markedly anemic. One of us (Walters) saw her in surgical consultation and did not feel that splenectomy was advisable. Roentgen examination showed varices of the lower third of the esophagus. On esophagoscopy examination, large veins were found involving the lower half of the esophagus. Sodium morrhuate was injected into these and the patient was permitted to go home, with instructions to return in three months for further examination. There was no retention of dye, and there has been no further bleeding.

CASE 4—The patient was a man aged 20 years. At 2 years of age he had severe malaria, and since then he had had an enlarged spleen. At the age of 8

years a diagnosis of splenic anemia was made and splenectomy was performed. One year after splenectomy the patient had his first gastrointestinal hemorrhage. Since then he had had repeated severe gastrointestinal hemorrhages, with loss of blood both by hematemesis and by bowel. Transfusions had been required frequently. In January 1939 ligation of the coronary vein was carried out, without marked benefit. The hepatic function test gave normal results. His blood volume had been kept low on purpose, in an attempt to prevent bleeding, but this had failed. Roentgen examination made here showed extensive varices involving the greater portion of the esophagus. Esophagoscopic examination likewise showed extensive varices involving most of the gullet. Repeated injections were carried out, and the patient was permitted to go home, with instructions to return for further examination in three months. He has had no further bleeding since the treatment.

CASE 5—A man aged 46 years gave a history of recurrent attacks of hematemesis and melena since Sept 25, 1938. He had had severe hemorrhages as frequently as every two weeks. Repeated blood transfusions had been required. The patient first came to the clinic in March 1939, and a diagnosis of esophageal varices was made. The spleen was not palpable at this time. Roentgen examination revealed esophageal varices involving the greater portion of the esophagus. Esophagoscopic study revealed large varices involving the lower half of the esophagus and the cardiac portion of the stomach. The patient was seen in surgical consultation, but operation was not advised. He continued to have bleeding and returned to the clinic in June 1940, at which time the value for hemoglobin was 48 per cent and the erythrocyte count 4,800,000 per cubic millimeter of blood. A test of hepatic function showed no retention of dye. When the first injection was attempted, the patient had a very severe hemorrhage and it was necessary to pack the esophagus. This controlled the bleeding nicely, and the patient recovered well. Further injections were carried out. While still under treatment he had a very severe hemorrhage, and at present he is in the hospital receiving transfusions. During the hemorrhage the value for hemoglobin was reduced to 9 per cent. Further injections are to be carried out because of his insistence and because of the fact that there is practically no alternative in his case.

CASE 6—The patient was a man aged 37 years. He first began to have melena and hematemesis in 1934. It is rather interesting that gastroscopic examination was made six times elsewhere in an effort to locate the cause of the bleeding but no bleeding point was found in the stomach, and no bleeding was produced as a result of the procedures. He first came to the clinic in 1934, when a diagnosis was made of hepatic cirrhosis with associated varices of the lower end of the esophagus. He has had repeated bleeding since that time, and repeated transfusions have been required. An interesting feature in his case is that he has had dye retention of grade 3 but that recently this has been only of grade 1. It has been only during the past year that the spleen has become slightly palpable. Roentgen examination showed varices involving the lower end of the esophagus. Esophagoscopic examination, however, showed the varices to run up into the upper third of the gullet. Injections have been given, with marked decrease in the size of the varices. The patient recently has had one very small episode of bleeding, and esophagoscopic examination since that time has revealed that a small vessel in the middle third of the esophagus had apparently leaked. Further injection of the sclerosing solution into this vessel has been carried out, and the patient has been getting along nicely.

We think that it must be emphasized that sufficient time has not elapsed to enable us to arrive at any definite conclusions as to the efficacy of this form of treatment. It may be pointed out that roentgen examination of the esophagus does not always demonstrate the varices. This is illustrated by a patient on whom one of us (Walters) recently performed splenectomy. In her case roentgen examination of the esophagus gave negative results, but on esophagoscopy examination we found large varices involving the lower third of the esophagus and almost occluding its lumen.<sup>23</sup> It is also of interest that the esophageal varices generally have been found to be much more extensive than the roentgenogram would lead one to believe. In practically all of the cases the varices were found to extend up into the upper third of the esophagus. It may also be pointed out that instrumentation can apparently be carried out without a great deal of danger of producing hemorrhage. This would seem to emphasize that trauma from the passage of food through the gullet is probably of only minor importance in the production of bleeding.

#### SUMMARY

Esophageal varices develop as a result of obstruction of the portal and splenic veins, and bleeding occurs because of their superficial position in relation to the esophageal mucosa. Although Banti's disease and splenic anemia are the conditions most frequently associated with esophageal varices, the former cannot be regarded as distinct clinical entities.

The surgical treatment of splenic anemia has been directed toward removal of the enlarged spleen on the assumption that it was contributing toward the destruction of red blood cells and, in addition, because splenectomy reduces the amount of blood flow to the portal vein by an amount ranging from a normal percentage of approximately 20 to a much larger percentage when the splenic vein and its branches enlarge with the enlargement of the spleen. In addition, in splenectomy the veins communicating between the splenic vein and the cardia and esophagus through the short gastric veins and gastroligament are interrupted by division and ligation, which assists in decreasing the amount of venous blood coursing through the esophageal varices. After removal of the spleen the denuded surface of parietal peritoneum forming its previous bed may be the site of formation of collateral veins between the portal and the caval system.

Although splenectomy performed for splenic anemia has been followed by good results in a large series of cases, it is apparent that

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<sup>23</sup> Although the spleen was about four times the normal size (weight, 910 Gm) in this case, with a considerable degree of splenitis, with fibrosis of the pulp and with marked phlebitis of the splenic vein and its branches, the liver appeared grossly to be normal.



this operation, even when combined with ligation of the coronary vein or with omentopexy, does not prevent recurrence of bleeding from the esophageal varices in more than 38 per cent of the cases. This is in keeping with the earlier reports of Mayo,<sup>12</sup> who said that "in about 10 per cent of the cases in which recovery has taken place after splenectomy, the patients have died some time in the next ten years of hemorrhage from the stomach, probably from ruptured varices in the lower end of the esophagus."

Although it has been shown that in the presence of portal cirrhosis a considerable flow of blood occurs through the coronary vein, which anastomoses with the internal mammary vein at the cardiac end of the stomach and in the esophagus and that ligation of this vein in the gastrohepatic omentum will serve to interrupt this flow of blood, this procedure has been used alone in too few cases of splenic anemia to justify any conclusion relative to its merits in reducing the incidence of hemorrhages from esophageal varices in such cases.

The recent successful obliteration of esophageal varices by the injection of sclerosing solutions into them through the esophagoscope and the report of 6 cases in which the injection was done at the Mayo Clinic give indication that this is a procedure worthy of trial to determine the permanence of its efficacy in causing obliteration of esophageal varicosities.

# ESOPHAGEAL DIVERTICULA

FRANK H LAHEY, M D

BOSTON

## HISTORICAL DATA

In 1764 Ludlow<sup>1</sup> observed "preternatural pockets" in the esophagus at autopsy

In 1816 Bell<sup>2</sup> published in his volume of "Surgical Observations" a paper entitled "A Praeternatural Bag, Formed by the Membrane of the Pharynx"

## CLASSIFICATION

In 1877, Zenker and von Ziemssen<sup>3</sup> were the first to classify diverticula of the esophagus into traction and pulsion types. They also made a study of the literature (23 cases) and added 5 of their own, in which autopsy was performed

In 1922, Bensaude, Gregoire and Guénaux<sup>4</sup> made a new classification of esophageal diverticula—those of the esophagus are distinguished from pharyngoesophageal diverticula

*Traction Diverticula*—In 1840, Rokitsansky<sup>5</sup> first correctly described traction diverticula

*Etiology*—In 1816, Bell<sup>2</sup> described the condition as due to distention of the pharynx from ineffectual attempts to swallow, with resultant protrusion of the inner coats of the pharynx through hypertrophied bundles of the inferior constrictor pharyngis muscle

In 1921, Kulenkampff<sup>6</sup> said that the condition is analogous to inguinal hernia and is produced by establishment of a sac in the site of a congenital muscular hiatus which is covered in with elastic tissue

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1 Ludlow, A. Obstructed Deglutition, from a Preternatural Dilatation of, and Bag Formed in, the Pharynx, M Obs Soc Physicians London **3** 85-101, 1762-1767

2 Bell, C. Surgical Observations, London, Longman [and others], 1816, pp 64-70

3 Zenker, F A, and von Ziemssen, H. Krankheiten des Oesophagus, in von Ziemssen, H. Handbuch der speciellen Pathologie und Therapie, Leipzig, F C Vogel, 1877, vol 7 (supp.), pp 50-87

4 Bensaude, R, Gregoire, R., and Guénaux, G. Diagnostique et traitement des diverticules oesophagiens, Arch d mal de l'app digest **12** 145-203, 1922

5 Rokitsansky, C. Spindelförmige Erweiterung der Speiseröhre, Med Jahrb d k österr Staates **21** 219-222, 1840

6 Kulenkampff, D. Zur Aetiologie, Diagnose und Therapie der sogenannten Pulsionsdivertikel der Speiseröhre, Beitr z klin Chir **124** 487-515, 1921

*Symptoms*—In 1900, Starck<sup>7</sup> divided symptoms into prodromal, direct and indirect

*Surgical Treatment*—In 1830, Bell proposed establishment of a fistula to empty the diverticulum of its contents, this was practiced in 1877 by Nicoladoni<sup>8</sup> in Vienna, Austria

In 1850, Kluge conceived the idea of excision, which was first done in 1884 by Niehans<sup>9</sup> on a patient with both goiter and esophageal diverticulum

In 1892, von Bergmann<sup>10</sup> reported a case of successful extirpation, and in the same year Kocher<sup>11</sup> performed the operation, with healing by first intention

In 1896, Girard<sup>12</sup> suggested a new method—invagination of the diverticulum and suturing of the esophageal walls

In 1917, Bevan<sup>13</sup> elaborated this procedure. He inverted the outer half of the sac and buried the stump with a series of purse string sutures.

In 1912, Schmid<sup>14</sup> proposed diverticulopexy, which was performed in 1917 by Hill<sup>15</sup> on a patient, with temporarily good results

From 1910 to 1915, the popularity of surgical treatment was inhibited by the high mortality associated with one stage procedures

In 1909, Goldmann<sup>16</sup> performed two stage operations, the pouch was freed, its pedicle ligated with silk, the wound packed and the sac fixed to the surface of the wound. This procedure resulted in sloughing of the diverticulum, and on the eighth day a fistula formed, which healed in two months

7 Starck, H. *Die Divertikel der Speiseröhre*, Leipzig, F. C. W. Vogel, 1900

8 Nicoladoni, K. *Behandlung der Oesophagusdivertikel*, Wien med. Wchnschr. **27** 606-607, 1877

9 Niehans, cited by Zesas, G. *Beitrag zur chirurgischen Behandlung des Speiseröhren Divertikels*, Deutsche Ztschr. f. Chir. **82** 577, 1906

10 von Bergmann, E. *Ueber den Oesophagusdivertikel und seine Behandlung*, Arch. f. klin. Chir. **43** 1-30, 1892

11 Kocher, T. *Das Oesophagusdivertikel und dessen Behandlung*, Cor.-Bl. f. Schweiz. Aerzte **22** 233-244, 1892

12 Girard, C. *Du traitement des diverticules de l'œsophage*, Assoc. franç. de chir. Proc. verb. **10** 392-407, 1896

13 Bevan, A. D. *Pulsion Diverticulum of Esophagus*, S. Clin. Chicago **1** 449-457, 1917

14 Schmid, H. H. *Vorschlag eines einfachen Operations-verfahrens zur Behandlung des Oesophagus-divertikels*, Wien klin. Wchnschr. **25** 487-488, 1912

15 Hill, W. *Pharyngeal Pouch Treated by Diverticulopexy*, Proc. Roy. Soc. Med. (Sect. Laryng.) **11** 60, 1917-1918

16 Goldmann, E. E. *Die zweizeitige Operation von Pulsiondivertikeln der Speiseröhre*, Beitr. z. klin. Chir. **61** 741-749, 1909

In 1916, Murphy<sup>17</sup> improved this method by implanting the sac in the wound with its neck unligated, thus preventing sloughing, and resected it two weeks later

In 1918, Judd<sup>18</sup> reported a modification of this method, the edges of skin were sutured to the neck of the sac, the wound was closed, and

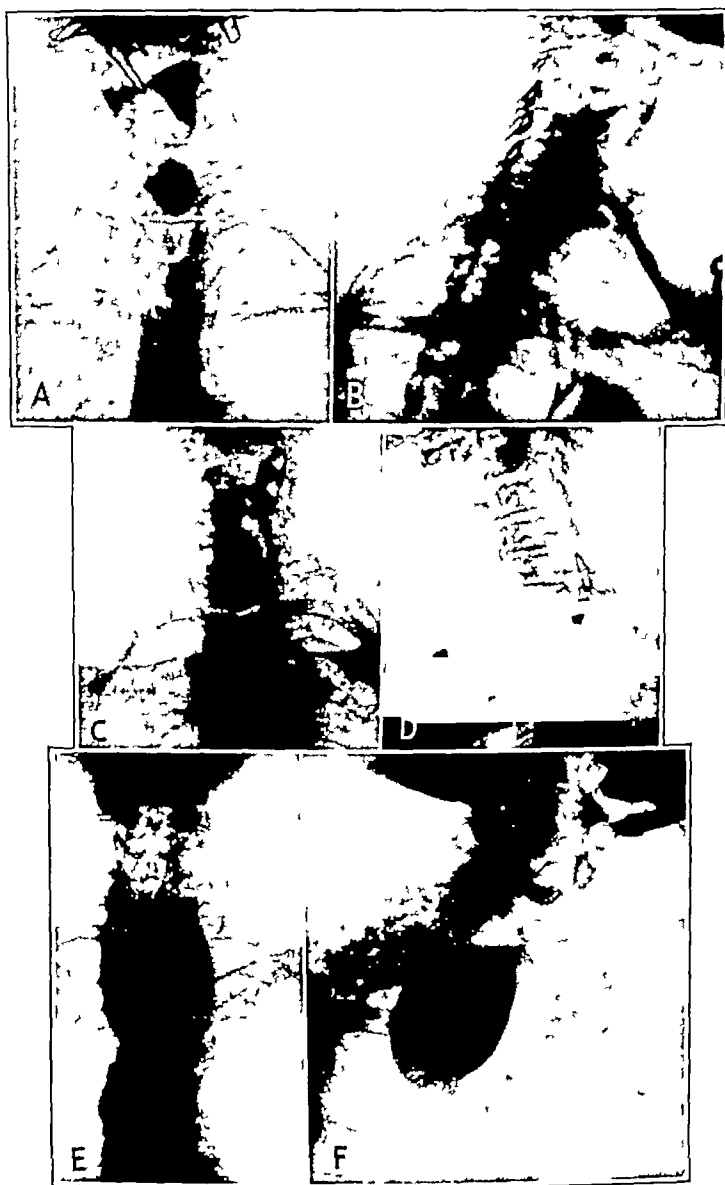


Fig 1—*A* and *B*, examples of the small type of pharyngoesophageal pulsion diverticulum. *C* and *D*, examples of the intermediate type. *E* and *F*, examples of the large type.

17 Murphy, J. B. Diverticulum of Esophagus. Conservative Treatment, *S Clin Chicago* 5:391-395, 1916.

18 Judd, E. S. Esophageal Diverticula, in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 15.

the sac was left as in an unopened colostomy stoma, lying on the skin. Ten to twelve days later, when healing had taken place within the wound and about the neck of the sac, it was cut away and its edges turned into the esophagus.

In 1933, I<sup>19</sup> modified the two stage operation. In small sacs the tip of the sac after dissection was sutured to the sternohyoid muscle at

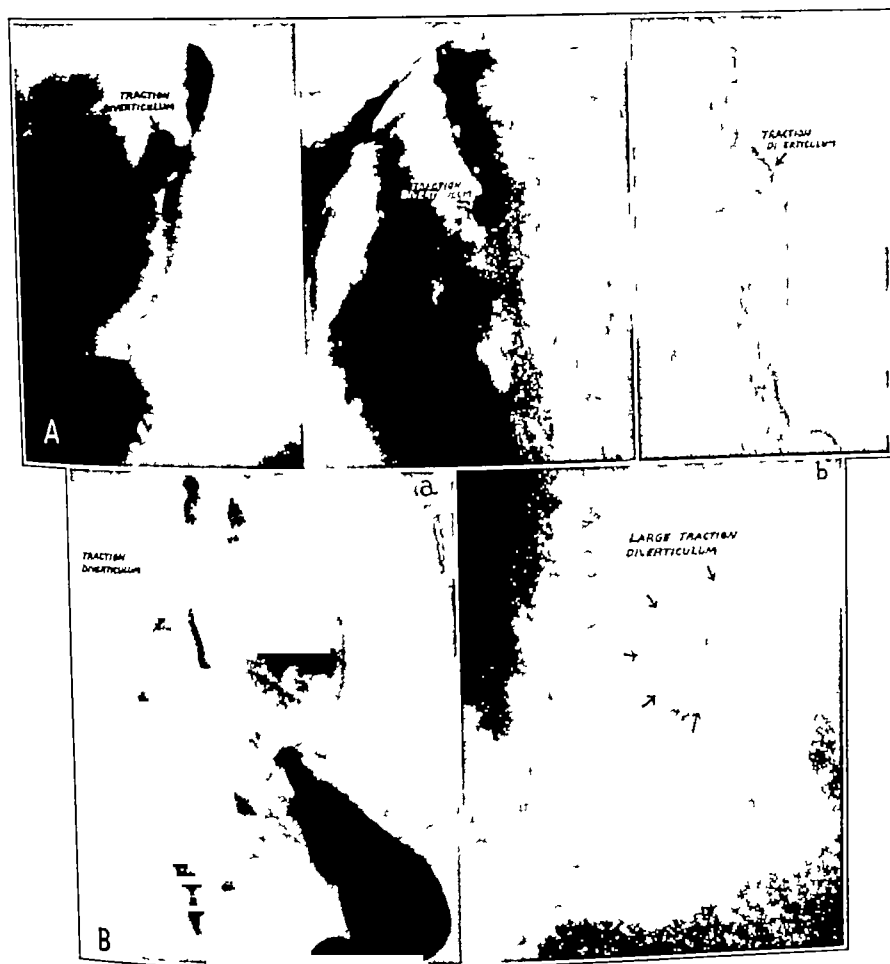


Fig 2—A, three examples of traction diverticula. Note the tendency of these diverticula to be pulled out laterally and not in a dependent position. B, further types of traction diverticula. Roentgenogram a represents the laterally pulled diverticulum, and roentgenogram b, the largest and most dependent type of traction diverticulum ever seen at this clinic. All of these have been handled satisfactorily by dilation. Note in roentgenogram b that, even though the diverticulum is of considerable size, the size of its opening into the esophagus is nearly half that of the complete diameter of the diverticulum, thus making it easily possible to empty itself

a level higher than its neck within the wound, and in large diverticula the sac was implanted in the wound, pointing upward. This prevented food from entering the wound between stages and caused the fistula which occurred after the second stage to close early.

Esophageal diverticula divide themselves into two main types, true diverticula, represented by the traction type of sac made up of all the

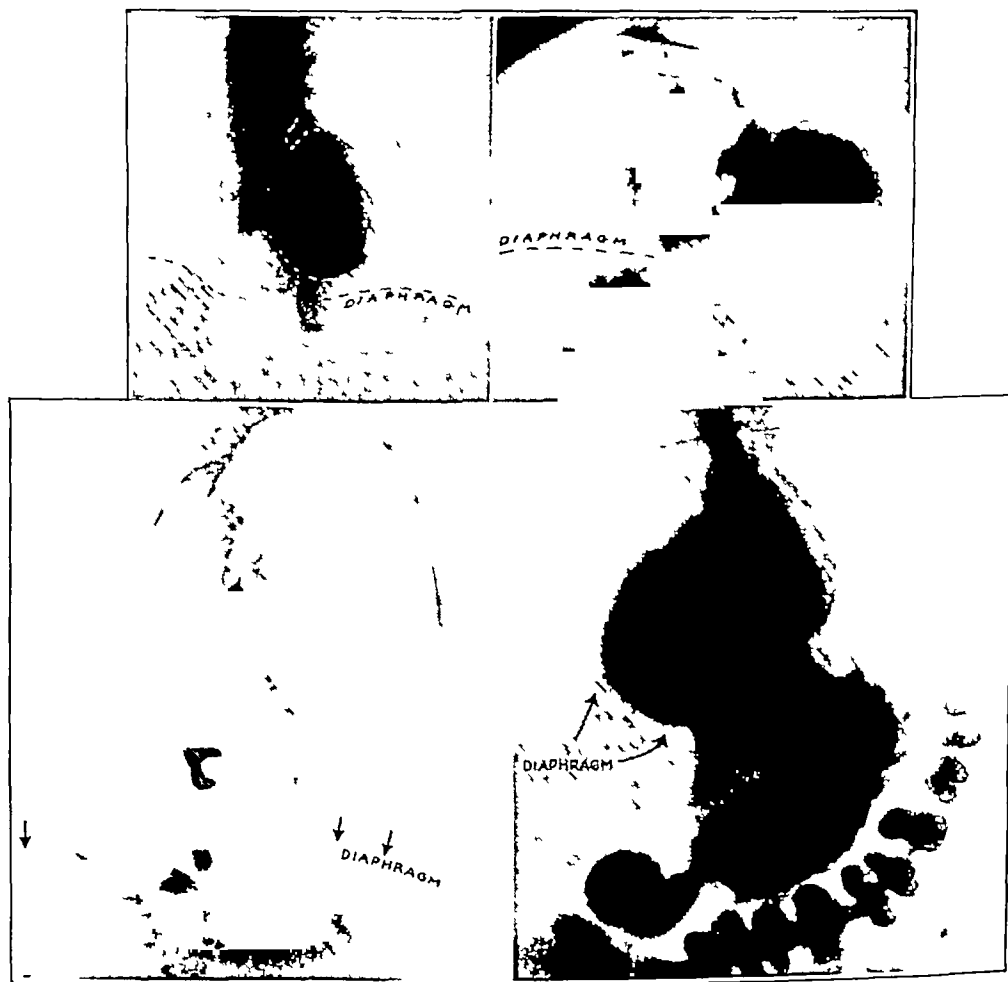


Fig 3—Supradiaphragmatic pulsion diverticula. The chief complaint in cases of this type of diverticulum is regurgitation of the foul contents of the sac, bringing about nausea together with regurgitation of the contents of the sac into the throat during sleep and thus waking the patient.

coats of the esophagus, and false diverticula, represented by the pulsion type so commonly seen at the pharyngoesophageal junction and so named the pharyngoesophageal diverticulum.

Esophageal diverticula occur at three levels: those at the pharyngoesophageal junction, represented by the pharyngoesophageal pulsion diverticulum (fig 1), those in the intrapleural portion of the esophagus,

particularly at the level of the main bronchial stem, represented by the traction diverticulum (fig 2) and those just above the diaphragm, the pulsion type (fig 3) By far the most common type and certainly the type most prone to produce troublesome symptoms is the pharyngo-esophageal diverticulum

#### PHARYNGOESOPHAGEAL DIVERTICULUM

The pharyngo-esophageal diverticulum has been well described as corresponding in its origin to an inguinal hernia It is a true herniation of mucosa and submucosa through the lowest fibers of the inferior con-



Fig 4—Diagrammatic illustration of the posterior aspect of the junction of the pharynx and the esophagus The two points marked *x* represent the two levels at which pulsion diverticula herniate through—the upper *x* is in the lowest fibers of the inferior constrictor muscle, and the lower *x* is at the pharyngeal dimple, the defect in the posterior wall where the cricopharyngeal muscles diverge from the lowest fibers of the inferior constrictor muscle

stricter muscle as they run transversely or through the obliquely dividing fibers of the cricopharyngeal muscles on the posterior aspect of the esophagus (fig 4) As the cricopharyngeal muscles spread off from the last fibers of the inferior constrictor muscle to become longitudinal and envelop the esophagus, they leave on the posterior wall of the esophagus a weak point, bounded above by the most inferior fibers of the lowest constrictor muscles and laterally by the obliquely descending fibers of the cricopharyngeal muscles This leaves a point or dimple

on the posterior wall of the pharynx at the cricopharyngeal junction unsupported or weakly supported by muscular covering

It has been suggested, owing to an incoordination between the impulses of the inferior constrictor muscles and the cricopharyngeal muscles, that material as it is propelled downward by the constrictors is resisted in its descent by any uncoordinated action of the cricopharyngeal muscles, thus tending to produce a bulging through this weak point

It is probable that in some persons there is at this point, as is true with inguinal hernia, a congenital weakness in muscular covering. Taken together with neuromuscular incoordination, this results in bulging of the mucosa and submucosa at this weak point, just as such bulging occurs through a weak inguinal ring in the early stages of an inguinal hernia. At this period the first stage of the pharyngoesophageal diverticulum occurs, diagrammatically shown in insert 1 in figure 5 *a* and, as

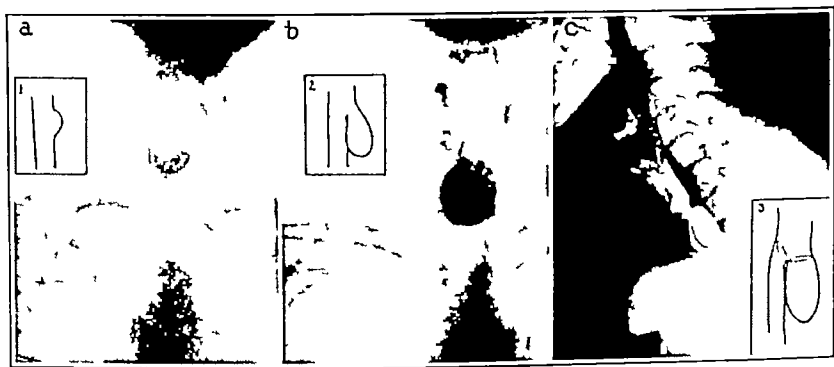


Fig 5—Roentgenogram *a* demonstrates the smallest type of esophageal diverticulum in its very earliest stage. Note that at this stage the sac has no neck. In insert 1 may be seen diagrammatically the early stage, in which the submucosa bulges through the fibers of the inferior constrictor muscle without as yet having produced a sac possessing a neck. Roentgenogram *b* represents a fully developed esophageal pulsion diverticulum with a definite neck, it is now at an operable stage. Note (insert 2) the diagrammatic illustration of the relation of the false opening into the diverticulum to the true opening into the esophagus. Note that the opening into the esophagus is in the lateral position at this stage, so that food still passes readily through the transverse opening into the true esophagus without difficulty. Roentgenogram *c* represents the stage of development in the esophageal diverticulum in which, owing to traction on the sac, the opening into the diverticulum (insert 3) is transverse and the opening into the esophagus lateral. One can appreciate from this diagram how food passes more readily into the diverticulum sac than into the esophagus and how traction with swallowing on the food-filled sac pulls the lips of the laterally placed opening into the esophagus together, which interferes further with the entrance of food into the true esophagus.

seen in an actual case, shown in the roentgenogram (fig 5 *a*). At this period of development of the diverticulum no semblance of a sac is present, only a teatlike projection of mucosa bulges between the oblique



fibers of the cricopharyngei muscles and the almost transverse fibers of the inferior constrictor muscle

At this period of development appears the earliest symptom associated with esophageal diverticula, solely the feeling of a piece of food stuck in the throat, causing an annoying cough in an endeavor to get it up. This is undoubtedly due to crusts of bread, flakes of cereal or any other dry bits of food lodging within the teatlike projection of mucosa, producing the same disagreeable discomfort as may be produced by a particle of food remaining persistently lodged in any portion of the pharynx.

As at this stage there is no neck to the sac, no operation should be considered. In my early experience with diverticula I have explored such diverticula at this stage and have not been able to undertake satisfactory operative repair. Since patients with diverticula at this time have no obstructive symptoms, no symptoms of regurgitation and only those symptoms occasionally brought about by particles of food lodging in the sac, there is no immediate necessity for operation, and one can with safety wait for further development of the sac. Wide and frequent dilation of the diverticulum at this period delays the development of the sac by dilating the fibers of the cricopharyngei muscles at the lower part of the neck of the sac. In the experience of this clinic this does not, however, prevent the ultimate occurrence of a progressively enlarging diverticulum with a well developed sac and neck.

In figure 5 *b* may be seen the completely formed diverticulum sac with a well developed neck and a dependent sac. This stage represents further advance from the first, or teatlike, stage and complete herniation of the pharyngoesophageal mucosa and submucosa between the most inferior fibers of the lowest constrictor and the oblique fibers of the cricopharyngei muscles. It represents the development of a true hernial sac, comparable with the sac of a fully developed oblique inguinal hernia.

In this second stage of the development of a pulsion pharyngoesophageal diverticulum it is to be noted (fig 5 *b*) that while the fully developed sac is still moderately small the opening into the sac is in the oblique direction on the lateral wall of the esophagus, and the opening into the true esophagus is still in the transverse position. This is of importance because at this stage a large portion of the food still passes satisfactorily by the lateral opening of the esophagus into the diverticulum and descends along the longitudinal esophagus into the stomach without obstructive symptoms.

As this stage the only inconveniences suffered by the patient are those related to the accumulation of food and mucus within the sac. There is frequently regurgitation of food eaten at a previous meal, mixed with mucus. At this stage the patients frequently complain that as they swallow food gurgling noises may be heard in the throat, due to the movement of the ascending and descending sac agitating the air mixed with

fluid and food within the sac. Patients at this stage not infrequently present themselves for operation because, they state, as a result of these noises they are objects of curiosity on the part of those who have meals with them. They frequently complain that their companions at meals are curious as to what causes the noises in the throat when they swallow.

Stage 3, illustrated in figure 5 *b*, and insert 3, represents the most advanced stages of a pharyngoesophageal diverticulum. At this stage the sac has become large and frequently has descended into the mediastinum. Downward traction on the food-filled sac converts the sac opening (fig 5 *c*, roentgenogram and insert) into a transverse one. Downward traction on the sac so angulates the esophagus that the direct course of descent of food is into the diverticulum itself, this tends not only to enlarge the sac but to force it by the weight of its retained food and by the traction on the food-filled sac with swallowing always in a downward direction into the mediastinum. As the large sac descends into the mediastinum and angulates the esophagus, it likewise angulates the true opening into the esophagus, so that it assumes a lateral position due to traction of the food-filled sac on the lateral esophageal wall. This true opening into the esophagus tends to have its lips so pulled together that, as it is viewed through the esophagus, the opening into the true esophagus is frequently represented only by a longitudinal slit. This accounts for the often encountered difficulty of passing an esophagoscope by the sac into the true esophagus. It is at this stage that obstructive symptoms tend to appear, since the first food swallowed fills the sac, makes traction on the now laterally placed true opening to the esophagus and tends to close it. Food then finds its way with difficulty through this opening into the true esophagus and thence into the stomach.

When I first began to deal with esophageal diverticula, because the food-distended sac pressed on the lateral wall of the esophagus it was my impression that the obstructive symptoms related to esophageal diverticula were largely caused by this mechanical pressure. I was unaware of the real cause of obstruction until esophagoscopy study of a number of patients demonstrated that the opening into the diverticulum itself was a true transverse one and that the opening into the true esophagus was laterally placed, with its lips so pulled together that food could not pass into it.

In the early stages of esophageal diverticula the symptoms are of insufficient magnitude to cause the patients seriously to consider seeking operative intervention. Many diverticula on which my associates and I have operated have undoubtedly existed for a number of years without their presence having been discovered either by the patient or by the physician.

One of the reasons that the patients come to operation is that they have been made unhappy by regurgitation of previously eaten food.

from the diverticulum sac, not infrequently on awkward and unexpected occasions. They have requested operation, as has been stated, not infrequently because they have been annoyed by the attention directed to them as they ate as the result of the gurgling within the sac due to air mixed with fluid as the sac ascends and descends with deglutition. They have also not infrequently sought surgical relief because the fluid-filled sac has spilled over at night when they were asleep, the fluid contents of the sac trickling down into the larynx and awakening them with violent coughing. As the result of this experience, 2 patients have inhaled such amounts of material spilled from the sac that abscesses of the lung have resulted, requiring preliminary drainage before operation on the esophageal diverticulum could be carried out. A large number of patients have, of course, sought operation because they have reached the third stage of the development of an esophageal diverticulum, with complete obstruction or ability to get little, if any, food into the stomach.

It is of interest to state, I believe, that fewer and fewer patients with very large esophageal diverticula are coming for operation, because physicians are becoming more familiar with the diagnosis of this condition, are more aware of the danger of delay in treating it and have developed greater confidence in the safety of its operative correction. The patients are now being sent for operation at much earlier stages, while the sacs are reasonably small.

A few patients have come to operation with complicated situations. Three have been operated on whose diverticulum sacs had been perforated elsewhere, before they came to this clinic, by either an esophagoscope or an esophageal dilator, serious mediastinitis resulting. One required posterior mediastinotomy, and 2 required gastrostomy and drainage of the mediastinum anteriorly before they recovered from the resulting mediastinitis. In spite of the fact that one would expect a great many adhesions in the mediastinum and about the neck of the sac to follow such an inflammatory reaction, this was not the case, and dissection of the sac was accomplished in these patients with little more added difficulty than in those cases in which no previous mediastinal infection and infection of the fascial plane had taken place. None of these patients, however, were operated on earlier than several months after recovery from the mediastinitis and cervical cellulitis.

One patient had a carcinoma of the esophagus limited to the body of the diverticulum sac (fig 6). Resection of the sac by the two stage method, together with a considerable portion of the adjacent esophagus, resulted in a most satisfactory outcome. The case is, however, of too recent origin for one to make any statement as to nonrecurrence of the carcinoma. The wound has healed completely, the esophagus has been dilated, and the patient is swallowing well. It was necessary in this case,

because of the amount of esophagus which was removed together with the sac and its neck, to feed the patient through a Levine tube inserted into the stomach through the nose

It has frequently been advised that patients with complete obstruction resulting from large mediastinal diverticulum sacs be submitted to preliminary gastrostomy. This is undoubtedly a wise procedure in cases in which obstruction to the esophagus has been present for a considerable

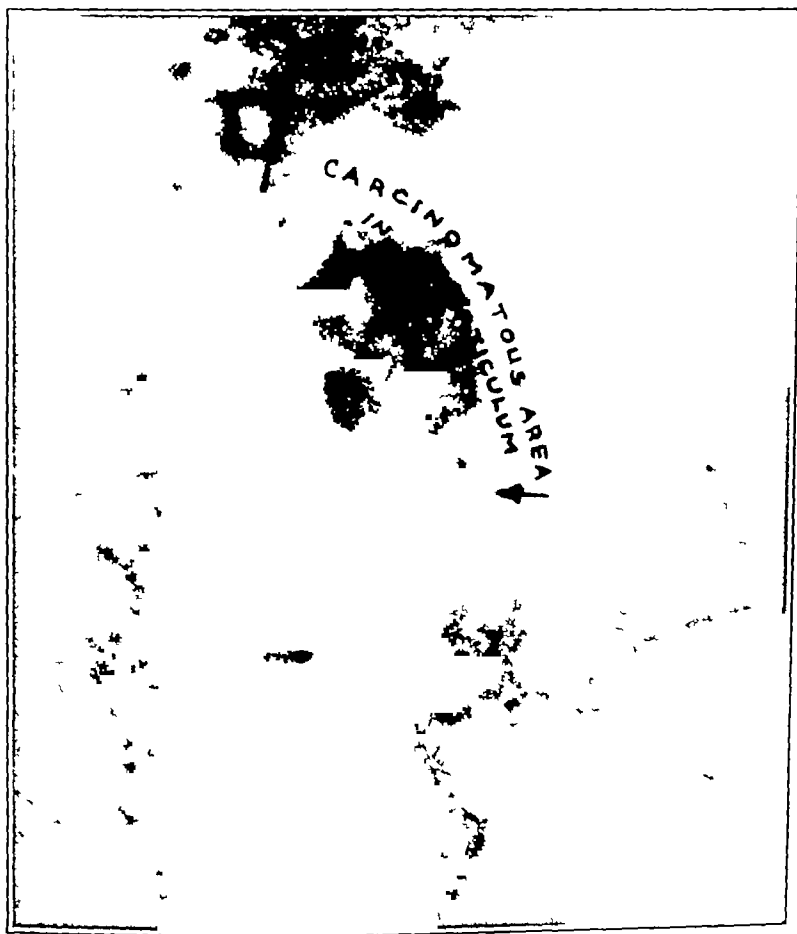


Fig 6—Roentgenogram demonstrating the occurrence of carcinoma arising in the mucosa of the lining of the diverticulum sac and limited to the diverticulum. Not only was the diverticulum sac with its contained carcinoma removed in this case, but in order to obtain a wide margin of safety a considerable portion of the wall of the true esophagus was also removed

period, with marked loss of weight, dehydration and general inanition. It is not necessary, however, in cases in which there is only incomplete interference with passage of food through the esophagus into the stomach. I have suggested and practiced (fig 9) the plan of completely dissecting the large sacs, implanting them in the wound and then inserting a feeding tube through a purse string suture in the dome of the sac. With

the tube sutured into the sac it may be guided down the esophagus into the stomach, and feeding may be immediately begun without the added complication of a gastrostomy

One can, of course, introduce a nasal catheter while the cervical wound is open, guide it past the sac into the esophagus after the sac has been freed and feed the patient in this way. It is far more comfortable for the patient to have the feeding tube introduced through the dome of the sac and into the esophagus, resulting in less irritation and discomfort than is the case when a nasal tube is left in the esophagus for a number of days.

The type of anesthesia employed in the operative treatment of esophageal diverticula is of considerable importance. My associates and I have employed regional and cervical block anesthesia in nearly all of these cases, because with the spilling of sac contents with operative handling of the sac it is so important for the patients to retain their throat reflexes to prevent pulmonary infections due to aspiration of these contents. In addition, this type of anesthesia is desirable because, with the patient conscious, he can be asked to swallow and thus make the sac ascend and descend, so that it can easily be visualized and dissected from below anteriorly, from above and along its opposite posterior wall.

There has been a good deal of debate at medical meetings and in the literature, as with so many other surgical procedures, as to whether one should employ the one stage operation in which the sac is completely dissected and its neck transfixed, ligated or sutured or the two stage procedure about which I have frequently written, in which at the first stage the sac is completely dissected, implanted high in the wound or in the skin and removed at the end of eight to ten days, when the fascial planes and mediastinum have been walled off.

There will always be differences of opinion regarding one stage and two stage operative procedures. They will be settled by a variety of circumstances—the extent of experience of the surgeon dealing with these cases, the type of cases with which he has to deal, the individual surgeon's ability and equipment to handle such cases, and the temperament of the person responsible for the patient, in terms of caution and responsibility.

I have repeatedly stated that I feel sure that the one stage procedure can be done with reasonable safety but that in a large series of cases the mortality rate, however small it may be in both groups, will be somewhat more favorable in the group done in two stages. It has always been my feeling that I am less interested in saving the patient's time than I am in saving the life of that last patient that makes up even a very small mortality percentage. I have now operated on 118 patients for esophageal diverticula. There has been but 1 fatality in the entire series, and that

in a man of 81 This patient died not of the operation for his diverticulum but of uremia Nevertheless, I am convinced that mortality as related to operative procedures cannot be explained away and that it must always be attributed to the operation Should a patient die of pneumonia either in the one stage or the two stage procedure, of emboli or of any other complication other than one directly related to the operation, it must, I believe, in all fairness and in order that one may correctly evaluate procedures, be attributed to the operative method

In view of the fact that I have been able to deal satisfactorily with 118 of these patients, with but 1 fatality, it would be difficult for anyone to convince me of the wisdom, for me at least, of employing the one stage procedure

As one compares the results and the thoroughness with which the operation can be done with either the one stage or the two stage procedure, there is little to be said in favor of either as relates to this aspect, One can dissect the sac and amputate the neck of the sac as completely in one as in the other As far as reenforcing the muscular defect over the mucosa goes, in the one stage operation the muscles over the diverticulum are so flimsy that even though they can be sutured in the one stage operation I doubt that they add much in the way of support over the ligated neck

With the exception of the method employed in 5 cases, in which the sac was completely dissected and suspended (fig 9) and in which, owing to the condition of the patient, the second stage was not performed, all of the operations reported on here have been done in two stages One patient died of pneumonia one month after discharge from the hospital The remaining 4 patients, on whom the second stage of the operation was not performed, are in satisfactory condition at the end of six years, seven months and six months (2 patients) respectively

I have repeatedly described the technic which I have employed in cases of esophageal diverticulum I have employed a long longitudinal incision in front of the sternocleidomastoid muscle This has been used in preference to a transverse goiter incision as advocated by others, because it gives wide exposure of the area to be dissected and because it permits high implantation of the sac and favors accurate and anatomic demonstration of all the structures to be dealt with Any one who has operated on many of these pharyngoesophageal diverticula will be conscious of the fact that the success of this operation is related to the thoroughness with which the neck of the sac is completely freed of all of its covering muscle fibers Unless the acute angulation of the neck of the sac is so completely freed that as the sac is carried upward this acute angle is converted into an obtuse one, the dissection is not complete Unless all muscle fibers have been so removed that the pale white submucosa of the neck of the sac presents itself plainly, dissection has

not been complete. Unless the slinglike muscle fibers beneath the lowest angle of the neck of the sac have been slit there will constantly be a tendency toward recurrence of the sac at this point. It is, therefore, evident that no incision which in any way limits exposure is desirable in this operative procedure, fraught as it so often is with possibilities of serious technical complications, such as perforation of the sac, incomplete dissection of its neck, hemorrhage from the inferior thyroid artery, injury to the recurrent laryngeal nerve, tears in the internal jugular vein and injury to the superior cervical sympathetic ganglion, with the production of Horner's syndrome.

For the foregoing reasons it has always been the conviction of this clinic that the safety which results from adequate exposure and anatomic dissection in a field in which bleeding can be accurately controlled far outweighs the question of the appearance of the scar.

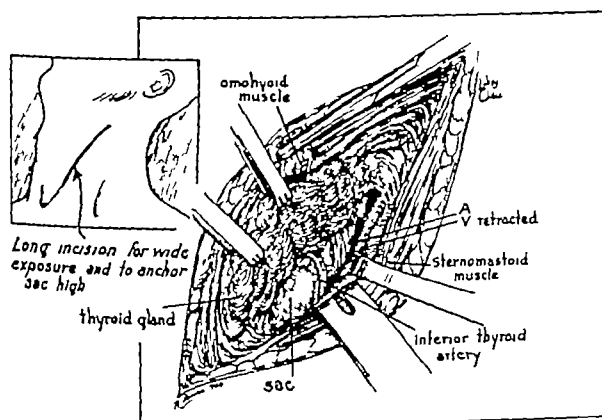


Fig 7—This and the following illustrations (8 and 9) demonstrate diagrammatically the technical procedures which have been employed in this clinic and some of which I have devised in the surgical treatment of pharyngoesophageal pulsion diverticula. In the insert may be seen the longitudinal incision in front of the sternocleidomastoid muscle. In the main illustration, the incision has been deepened so that the omohyoid muscle has already been severed, the internal jugular vein and the common carotid artery retracted, the thyroid gland mobilized toward the median line and the inferior thyroid artery with the sac of the diverticulum beneath it exposed. This illustrates also how necessary it is to divide the inferior thyroid artery in order that the sac beneath it may be dissected and mobilized.

The operative technic is well shown in the technical illustrations (figs 7, 8 and 9). The longitudinal incision in front of the sternocleidomastoid muscle is carried through the skin down to the sternocleidomastoid muscle. This muscle is dissected back until the omohyoid muscle is well demonstrated. The omohyoid muscle is then severed at its upper attachment and at the point where it disappears beneath the sternocleidomastoid muscle, it is amputated at this point, and its stumps are

tied With the omohyoid muscle out of the way, the thyroid gland is separated from the internal jugular vein and the common carotid artery, and the thyroid gland is picked up with blunt retractors and pulled toward the middle line The inferior thyroid artery is then demonstrated deep in the neck, cut between forceps and ligated Good-sized diverticulum sacs descend into the mediastinum beneath the inferior thyroid artery, so that it is necessary that that structure be severed in order that the delivery of such deep sacs may be safely accomplished After the inferior thyroid artery has been tied and the lobe of the thyroid elevated, if the patient is asked to swallow the sac of the diverticulum will immediately be seen to ascend and descend In most cases the sac will be closely bound to the longitudinal esophagus by the enveloping fibers of the cricopharyngei muscles These are separated at the lowest

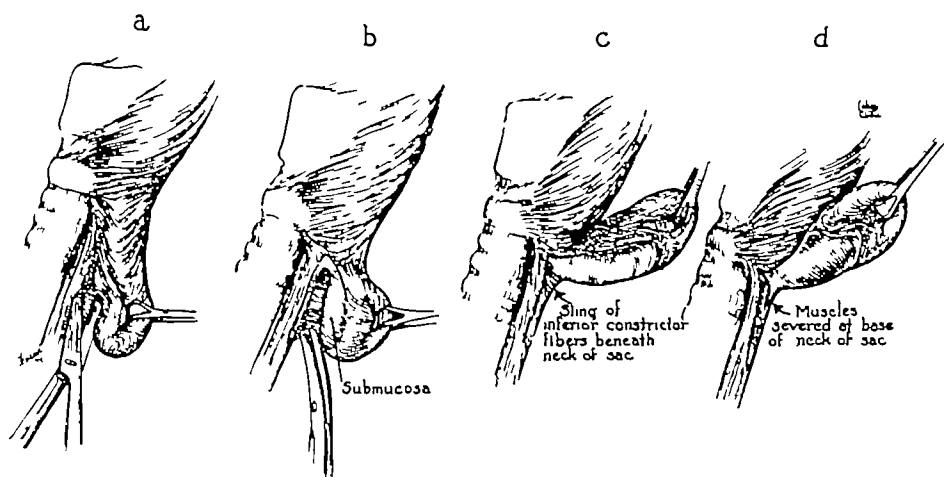


Fig 8—In illustration *a* may be seen diagrammatically the plan of separating the dependent sac of the diverticulum from the longitudinal esophagus, to which it is adherent and over which run the enveloping fibers of the cricopharyngei muscles Note the sac grasped with the Babcock blunt forceps so that traction can be made on it to facilitate the separation In illustration *b* the anterior fibers enveloping the wall of the sac have been separated, and the posterior fibers are now being cut Note the appearance of the submucosa as the fibers running over the sac and enveloping it with the longitudinal esophagus are severed Note particularly (illustration *c*) that the sac has been completely dissected up to its neck and that the sling fibers of the inferior constrictor muscle immediately beneath the neck of the sac have as yet not been severed It is failure to sever these sling fibers that is so apt to bring about production of a shelf by means of which food is caught and recurrence of the herniation encouraged In addition to this, failure to cut these sling fibers makes it impossible to mobilize the sac upward so completely that what was an acute angle at the lower aspect of the neck can be adequately converted into an obtuse angle In illustration *d* may be seen the completely freed submucosa and the incision of the sling fibers of the inferior constrictor muscle immediately beneath the neck of the sac This diagrammatic illustration demonstrates the completely mobilized sac with its submucosa and all of the muscle fibers about the neck of the sac freed and cut It is now ready to be implanted high in the neck



angle of the sac, and the dome of the sac is grasped with blunt Babcock forceps. The neck of the sac is then completely dissected.

As already has been stated, great care must be exercised in working out the line of cleavage between the inner lateral wall of the diverticulum sac and the outer longitudinal wall of the esophagus. Once this is established the dissection immediately becomes easier. As the sac is gradually dissected upward and freed it will become evident that, while the attachment of the lateral wall of the sac to the longitudinal esophagus in front has been freed, it is still bound down by the overlying muscle fibers in the back and behind the esophagus on the opposite wall. It is

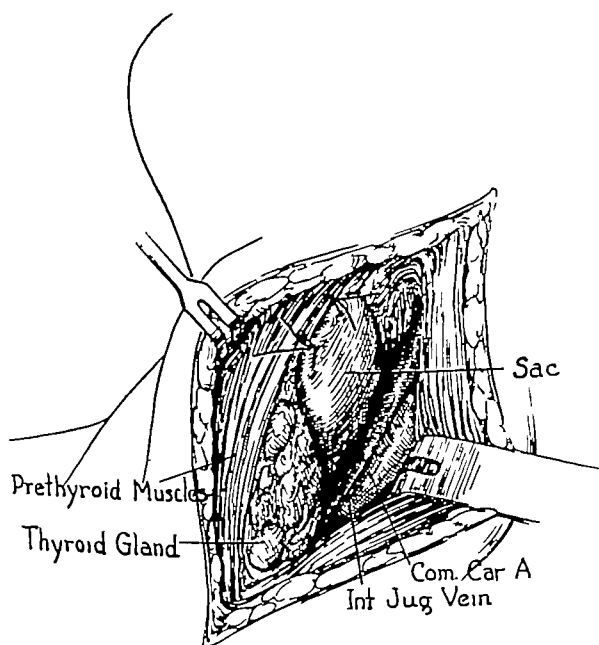


Fig 9—Plan by which the completely freed sac, as shown in illustration 8 *d*, is attached by black silk stitches through adventitious tissue over the wall of the sac to the prethyroid muscles in the neck at such a height that the dome of the sac is well above the level of the neck, thus preventing the entrance of food. After this, a gauze drain is inserted into the mediastinum, where it remains for four days. At the end of eight days, when the mediastinum and fascial planes are walled off, the wound is reopened, the dome of the sac is cut off, the mucosa is trimmed from within the sac, and the canal of submucosa without its mucous membrane (shown in this illustration) is preserved and packed with gauze. The gauze is removed on the fourth day, when the wound collapses and the submucosal canal usually closes with no drainage.

at this point that wide exposure is so necessary, since unless the muscles covering the sac which run behind the esophagus to the opposite side are freed it will not be possible to deliver the sac completely, so that it hangs entirely free by its neck.

With the sac hanging entirely by its neck it becomes extremely important to dissect with meticulous care all of the muscle fibers about the neck of the sac and particularly those fibers acting as a sling at the most inferior angle of the neck of the sac (fig 8 *c*). With the sac so completely dissected that it hangs freely by its neck with all overlying muscle fibers detached, with the slinglike muscle fibers under the lower angle of the neck of the sac slit and with the white submucosa of the sac neck clearly visible (fig 8 *d*), the dissection is complete. The sac is then carried upward over the upper pole of the thyroid and pinned by two black silk stitches to the uppermost fibers of the sternohyoid muscle. Care is to be taken in inserting these two black silk stitches that the needle does not pass through the wall of the sac but only through the adventitious tissue about the sac. If the needle is passed through the wall of the sac the stitches will cut out as a result of traction on the sac during swallowing, and there will be contamination of the wound and serious secondary infection in it.

When my associates and I first began to suspend these small sacs temporarily to the edge of the sternohyoid muscle within the wound merely by inserting black silk stitches through the adventitious tissue about the dome of the sac, we were fearful lest this rather delicate tissue would not keep the sac suspended in this position. There has never been any difficulty about this, in spite of the fact that with relatively small sacs there has undoubtedly been some traction on the sac. If the sac remains for two or three days fixed by the black silk stitches in this upward position it will become so adherent as a result of the exudate about it that even though moderate retraction from the stitches occurs the sac will be found at the second stage of the operation still in its proper location and pointing upward.

It is desirable to employ two black silk stitches to fix the dome of the sac to the sternohyoid muscles, leaving the ends about  $\frac{1}{2}$  inch (1.2 cm) long. By this plan, which I suggested a few years ago, it is possible to find the sac quickly when the wound is reopened at the end of eight to ten days. Prior to the employment of this plan, owing to the fact that the granulating wound frequently oozed considerably, it was often not easy promptly to locate the sac within the wound.

After implantation of the sac, the gauze end of a good-sized cigaret drain is inserted into the mediastinum to produce walling-off granulations and is left in place for four to five days. At the end of this time it is removed, and at the end of eight to ten days the second stage of the operation is undertaken, without danger of cellulitis or mediastinitis from contamination of the contents of the sac.

The patients are permitted to be out of bed on the afternoon of the first operation. They are permitted to swallow food and fluids

immediately, and because the tip of the sac is implanted higher than the neck (fig 9) food at once passes readily by the diverticulum opening into the true esophagus and so on down into the stomach. One can feed the patients on the table as soon as the first stage of the operation is completed and it can be demonstrated that any obstructive symptoms formerly present have completely disappeared.

At the end of eight to ten days, with the patient under intratracheal cyclopropane anesthesia (regional anesthesia or field block is not satisfactory because of the secondary reaction within the wound), the wound is reopened. The finger is inserted along the sinus still present at the lowest point of the wound, where the drain was removed. The edges of the skin are gradually pulled apart, and with a piece of gauze the sternocleidomastoid muscle, the internal jugular vein and the carotid artery are gently wiped outward throughout their entire course in the wound. With the wound widely opened, the black silk stitches demonstrating the tip of the sac are at once evident. The sac itself is then located, it is grasped with Allis forceps, the black silk stitches are cut out, and the sac is wiped out of the bed which it has molded for itself in the tissues until it is entirely free. The tip of the sac is then cut off, and the two layers, the mucosa and the submucosa, making up the wall of the sac immediately become plainly evident.

At the first stage operation the wall of the diverticulum sac will be almost as thin as a sheet of delicate writing paper, but at the second stage the submucosa will be so edematous that it will be of the thickness of a heavy sheet of blotting paper, and the submucosa will be found readily separable from the mucosa.

The submucosa may then be grasped with tacking forceps, and the mucosa can, with blunt scissors, be easily and completely separated from the canal of submucosa until it is entirely freed to the neck of the diverticulum. The mucosa is then cut off at the neck of the diverticulum, a small piece of gauze is inserted in the submucosal canal remaining. The drain is then brought out through the wound, buried stitches of plain catgut approximate the platysma and the subcutaneous fat, and the wound is closed with clips (fig 10). The advantage of retaining the submucosal canal freed of its mucosa is that the canal, which still points upward, collapses after removal of the drain from it, and this prevents postoperative drainage of food through the wound and establishment of a sinus.

The drain within the canal of submucosa is removed at the end of four to five days, and, provided it has been possible to retain the submucosa complete within the canal, there is usually healing without leakage.

Some of the operative complications which can occur and some which have occurred in the experience of this clinic require mention. One must be careful in dissections of the neck of the diverticulum sac, since it is to be recalled that the lowest fibers of the inferior constrictor muscles are attached to the horn of the thyroid cartilage and that this is the level at which the neck of the diverticulum sac is located. One must remember that it is beneath these lowest fibers of the constrictor muscles that the recurrent laryngeal nerve enters the larynx to become intralaryngeal. Care must be exercised, therefore, in dissections of the neck of the sac.

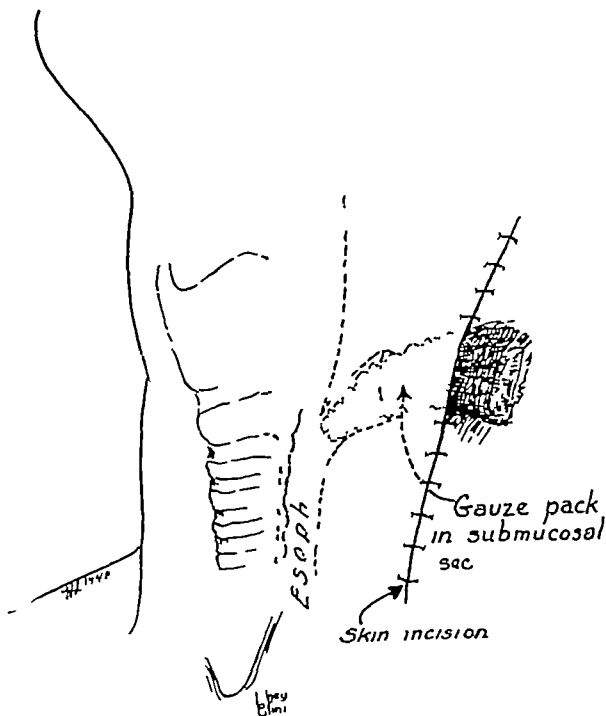


Fig 10—Diagrammatic illustration of the second stage of the operation, showing the gauze pack emerging into the upper part of the wound and placed through the submucosal canal, from which all mucosa has been removed. Note that the remaining submucosal canal points upward. When the gauze pack is removed, on the fourth day after operation, the canal will so collapse in its upward position that there will not be leakage of esophageal contents through it.

lest injury to the recurrent laryngeal nerve result. One must remember also that, as the common carotid artery and internal jugular vein are pulled back at the upper angle of the wound, not infrequently one comes in contact with the superior cervical sympathetic ganglion, injury to which will, of course, result in drooping of the lids and Horner's syndrome.

One must be careful with large sacs implanted in the wound with the tip of the sac above the level of the skin not to pull the sac too far out into the wound, lest the longitudinal esophagus be displayed

laterally and so acutely angulated that food cannot satisfactorily pass down its course. In my early experience this occurred to me, and on two occasions it required reopening of the wound and restoration of the dislocated esophagus to its midline position before adequate swallowing could be accomplished.

With large diverticula one must be careful to watch the sac implanted above the level of the skin within the dressing, because with the swallowing of food and air large diverticulum sacs not infrequently become so enormously distended and tense with air that gangrene can result. Should distention of the sac with air occur, a rubber catheter should, by means of a purse string suture, immediately be inserted into the sac through its tip to overcome this distention.

In no case in this entire series of 118 cases of pharyngoesophageal diverticulum has the sac, the neck of the sac or any level of the esophagus been perforated. I cannot, therefore, speak from experience as to what should be done should a perforation of the sac or of its neck occur during its dissection. I feel very strongly, however, that should it occur it should be carefully sutured with silk, with inversion of the point of perforation and accurate closure with lightly tied silk mattress sutures. I feel very strongly that, should leakage occur, there will always be the danger of contamination of the fascial planes and the mediastinum. In the event of this occurrence, large gauze packs should be inserted into the mediastinum and into the fascial planes behind the esophagus as a protection against the possible spread of the resulting infection downward toward the mediastinum, and, in addition, a feeding tube should be inserted through the nose into the stomach. One should not fail to recall that the esophagus with its diverticulum is in front of the prevertebral fascia and behind the pretracheal fascia and that this fascial plane leads directly into the superior mediastinum.

One cannot have operated on this number of esophageal diverticula without having dealt with almost all of the complications that can arise in connection with them. One of the most distressing is a persisting sinus through which food is discharged for several weeks after operation. Such a sinus is, in my opinion, most often the result of incomplete and inadequate dissection of the sac. It is most often the result particularly of inadequate dissections of the neck of the sac. If the angle shown in figure 8*b* is not completely freed so that it is converted into the angle shown in figure 8*d*, there will constantly be a ridge or shelf of mucous membrane which will catch food, discharging it outward along the sinus and thus keeping the sinus tract open. I can say from experience, however, that although I am sure that some of the sac necks in the operations mentioned were not dissected as completely in my early experience as I should today like to have them, none of the sinuses ultimately failed to close.

Recurrence took place in 3 of these cases, and reoperation was required. I am sure that the recurrences were the result of incomplete dissection of the neck of the sac before I had had the necessary experience with which to accomplish these painstaking dissections.

There has often been considerable debate as to whether patients with esophageal diverticula require postoperative dilation. A number of patients from considerable distances, operated on at this clinic, have not been able to obtain postoperative dilation and have had quite as satisfactory results as those on whom dilations have been done. This group, however, represents but a small proportion of the entire group, and so one cannot say with fairness that the results in all cases without postoperative dilation are as good as those in cases in which postoperative dilation is done. It has always seemed to me that one cannot carry out these operative procedures at the pharyngoesophageal junction either in one or in two stages without producing considerable scarring. Whether one does this operation in one stage or in two stages there must still be present a certain degree of muscular weakness at this level and perhaps some incoordination of the cricopharyngeal muscles, and for this reason it has always seemed wise to me when possible to do dilations after operation.

Postoperative dilation is done in this clinic by the laryngologists, a Plummer bag is used, and wide dilatation is carried out.

In reviewing my experience with pharyngoesophageal diverticula, my conclusions are: 1. At the very early stage, operation is not indicated. 2. It is desirable that these patients be submitted to operation once the sac is well formed, with a definite sac and a definite neck. It is undesirable to permit these sacs to reach such a size that they enter the mediastinum and produce obstructive symptoms. 3. The two stage operation in my hands satisfactorily fulfils the requirements of adequate removal of the sac with safety. 4. The most important technical features of the operation are that the neck of the sac be completely freed of all its muscular coverings until the pale submucosa is entirely visible about the neck of the sac, that the tip of the sac be so implanted upward that what was at first an acute angle at the inferior aspect of the neck of the sac becomes an obtuse angle so that food cannot be caught in it, and that the greatest care be exercised lest the sac or its neck be perforated during the dissection.

#### TRACTION DIVERTICULA

Figure 2 shows typical types of traction diverticula. These diverticula originate from inflammatory processes in adjacent bronchial lymph nodes. These inflammatory reactions become attached to the esophagus and, as cicatrization occurs, result in traction bands which pull the esophagus out in the lateral direction.

The symptoms associated with this type of diverticulum (traction) are rarely urgent. They consist largely of partial degrees of obstruction or interference with the progress of food and are as a rule promptly relieved by dilation.

Owing to the fact that most traction diverticula are pulled in either a lateral or an upward direction, they tend to empty themselves. Spontaneous emptying of these sacs is further favored by the fact that muscular contraction occurs within the walls of the sac. Since the walls of the sac are made up of all the coats of the esophagus, including the muscular coat, muscular expulsion of the contents of the sac is possible.

Operative treatment is not indicated for diverticula of this type and, if it were, would be extremely difficult to accomplish, since they are difficult to approach, located as they so often are at the bronchial hilus and not possessing necks. It must be recalled in surgical intervention on the esophagus that leaks are particularly apt to occur in esophageal suture, that the structure of the esophagus is not the best from the point of view of holding sutures, and that the blood supply of the organ is by no means profuse.

#### PULSION DIVERTICULA (SUPRADIAPHRAGMATIC)

The final type of diverticulum to be discussed is that shown in figure 3, the supradiaphragmatic pulsion diverticulum. These diverticula fortunately are extremely rare. In the fairly good-sized experience of this clinic with esophageal diverticula, only 4 have occurred.

These diverticula have well developed sacs with narrow necks, and their lateral walls tend to become adherent to the longitudinal esophagus, as do the lateral walls of the pharyngoesophageal pulsion diverticula.

The symptoms associated with the 4 cases of this type which have been observed in this clinic were related to decomposition of food which remained within such a large sac over a long period and regurgitation of such food during the night, interfering with sleep.

In a previous discussion of this type of diverticula, I described a conservative method of treatment which proved satisfactory. With the chest open and the lower lobe of the lung held out of the way, this type of diverticulum may be readily dissected so that it hangs freely by its neck. Owing to the fact, already stated, that the esophagus holds stitches badly and that amputation of the sac at its neck could be accomplished only at the risk of soiling of the pleural cavity, it was considered unwise in this case to attempt excision of the sac, and there appeared no plan by which it could be safely submitted to a two stage procedure.

The plan devised for this case and reported in 1933 consisted of fixing the dome of the completely freed sac with silk stitches high in the pleural gutter beside the vertebral bodies so that it was implanted

upward as a cord parallel to the longitudinal esophagus. The same principle was utilized in this procedure which is employed in the first stage operation for pharyngoesophageal pulsion diverticulum. With this plan the sac can be converted into a stringlike structure fixed by black silk stitches not passed through all of the walls of the sac and caught to the parietal pleura. With the sac so implanted high in the pleura beside the esophagus, food, as can be demonstrated roentgenographically, passes readily by the neck of the sac and can be made to enter the sac only when the patient is placed in the Trendelenburg position. This is a useful procedure to employ in these cases, by means of which the sac can be made to remain free from accumulated food without the hazard of pleural contamination by its removal.



# CONSERVATIVE TREATMENT OF ACHALASIA

ELMER B FREEMAN, M D

BALTIMORE

Success of conservative treatment of achalasia depends mostly on complete dilation of the cardia and not on drug therapy or dietetic management. Those interested in the conservative treatment of achalasia are in complete agreement that some type of dilation of the cardia is needed to overcome the obstruction, but there is a very wide difference of opinion as to the procedure by which this is to be accomplished. Each of the following methods has its advocates.

(1) Dilation with mercury-filled bougies, (2) dilation with bougies passed through the esophagoscope, (3) dilation with the combined mercury bougie and pneumatic dilator, (4) dilation with a pneumatic or hydrostatic dilator, and (5) dilation under fluoroscopic control.

It is not claimed by the advocates of any of the procedures that the dilated esophagus will return to normal after thorough dilation of the cardia, even though the obstructive symptoms have been completely relieved. As a matter of fact, it has been definitely proved that the dilated esophagus never regains its normal tone. But it is maintained by advocates of each of the procedures that the obstruction can be sufficiently overcome in most cases to permit the contents of the esophagus to pass freely through the cardia.

## DILATION WITH MERCURY-FILLED BOUCIES

The mercury-filled bougies as designed by Hurst consist of a number of rubber tubes of different sizes, each filled with the same amount of mercury, i e, 1 lb 5 ounces (609 Gm). The bougies range in size from approximately  $\frac{1}{2}$  inch (1.2 cm) in diameter to  $\frac{3}{4}$  inch (1.9 cm) or even more. After the bougie has been introduced into the esophagus, the weight of the mercury carries it through the cardia. Sometimes the bougie is passed under fluoroscopic control, when it is considered desirable to determine its exact relation to the cardia. In many cases it is necessary to introduce the bougie daily in order to control the obstruction and keep the cardia sufficiently dilated to permit the free passage of esophageal contents. In some cases of severe involvement it is necessary to introduce the bougie before every meal. This method has one very decided advantage, in that the bougie is easy to introduce and the patient may be readily trained to introduce it himself. After the treatment has been established, the size of the bougie and the frequency of introduction in many cases may be left to the discretion of the patient.

## DILATION WITH BOUGIES PASSED THROUGH THE ESOPHAGOSCOPE

Dilation of the cardia with bougies passed through the esophagoscope is not, in my opinion, a satisfactory procedure. First, it necessitates the introduction of the esophagoscope whenever it is deemed necessary to give a treatment. This in itself is an ordeal. With the esophagoscope in position, the introduction of a large bougie through the instrument so obstructs vision that one cannot keep the bougie under careful observation while it is being introduced. The main objection is, however, that it is impossible to pass a bougie of sufficient size through an esophagoscope to dilate the cardia completely, which is necessary if one is to overcome the obstruction and thus relieve the symptoms.

## DILATION WITH THE COMBINED MERCURY BOUGIE AND PNEUMATIC DILATOR

Browne and McHardy have recently devised a mercury bougie with a pneumatic dilator which embraces many of the good qualities of the Hurst, Plummer and Smithies instruments. They have frankly stated 'This dilator is not presented with the idea that it is applicable in all instances, any more than other instruments may meet all emergencies, but rather that it fills a need most frequently encountered.'

## DILATION WITH A PNEUMATIC OR HYDROSTATIC DILATOR

Dilation of the cardia with either a pneumatic or a hydrostatic dilator is, I believe, the most satisfactory method available at present to overcome the resistance at the lower end of the esophagus that is met with in cases of achalasia. In my opinion it does not make any material difference which method is used, it is a matter of personal preference. The dilating bag should be of sufficient caliber to dilate the cardia completely, and the dilator should be so designed that it may be easily introduced and will maintain its position in the cardia while the dilating bag is being distended. In my opinion, the Plummer modification of the Russell dilator, with either air or water used to distend the dilating bag, fulfils these requirements more satisfactorily than does any other instrument so far designed. Certain precautions, however, should be observed. First, one should pass a no. 60 French scale bougie over a previously swallowed, properly anchored thread as a guide. If a no. 60 bougie cannot be passed without difficulty, the probability is that the obstructive symptoms are due not to dysfunction of the lower end of the esophagus but to an organic lesion of the esophagus or an organic lesion of the cardiac end of the stomach encroaching on the cardia. It is therefore most important to determine whether a large bougie will pass easily through the cardia. If one cannot pass a large bougie, no attempt

should be made to introduce the Plummer dilator. It is also very important to pass the dilator over a previously swallowed, properly anchored size D silk thread. The size of the thread is likewise very important. Experience extending over many years has definitely proved that size D thread is the most satisfactory to use. For the thread to become properly anchored it is necessary to swallow 6 yards (5.4 meters) of it very slowly the night before the treatment is to be given. This permits the thread to work its way through the stomach and become anchored in the small intestine. The end protruding from the mouth should be fastened to the clothing, which makes it available when desired. After the treatment has been given, the thread is cut and permitted to pass on through the gastrointestinal tract. Nothing is given by mouth except water or weak tea from the time the patient starts to swallow the thread until the treatment is given. If these simple precautions are followed, one should not have any difficulty in introducing the instrument. It is not at all necessary to introduce the instrument under fluoroscopic control, as by the sense of touch one can easily tell when the instrument is in proper position. If it tends to slip downward into the stomach or upward into the esophagus when the dilating bag is being distended, it indicates a faulty position of the instrument, which can be readily corrected by releasing the pressure and changing the position as indicated. The number of dilations necessary to relieve the obstruction cannot be determined until after treatment has been begun. In many cases almost complete relief is obtained after one satisfactory dilation, in others several treatments may be required, and in an occasional one a treatment may be needed every month or two, or even at longer intervals, to keep the patient comparatively free of symptoms. The amount of pressure necessary to obtain relief of symptoms varies from the equivalent of 10 to 18 feet (3 to 5.4 meters) of water pressure or even more. The end results with the Plummer treatment are satisfactory in at least 75 to 80 per cent of the cases. In most of the remaining 20 to 25 per cent the patient is materially benefited.

#### DILATION UNDER FLUOROSCOPIC CONTROL

With few exceptions, there is no advantage in dilating the cardia under fluoroscopic control. However, if one is dilating the cardia with mercury-filled bougies, it may be helpful in determining the exact relation of the bougie to the cardia. If the dilator is introduced over a previously swallowed thread, there is no necessity for fluoroscopic control, as by the sense of touch alone one is able to determine when the dilator is in proper position. Dilation under fluoroscopic control necessitates working in a dark room, which, in my opinion, is a distinct disadvantage, in that one is not able to observe the patient while the dilation

is being done I have always relied very much on my observation of the patient while the dilating bag is being distended. By observation at that time one is able, in a measure at least, to determine how much pain the dilation is causing. The degree of pain produced is helpful in determining the amount of pressure to be used. If the dilation causes much pain, one should be very cautious and increase the pressure slowly at subsequent treatments.

#### LOCAL TREATMENT

No local treatment of the associated chronic esophagitis, which is present in practically all cases of achalasia of the cardia to a greater or less degree, is required. Just as soon as the cardia has been sufficiently dilated to permit the esophageal contents to pass readily into the stomach, the esophagitis promptly disappears. Of course, early in the treatment one may be justified in resorting to lavage of the esophagus if there is marked dilatation with retention, but even this is not necessary after one or two complete dilatations of the cardia.

#### DRUG THERAPY

The administration of drugs is of questionable value. While antispasmodic sedative drugs seem to help to a certain degree, I think that their beneficial results are due to their general sedative effect and not to any local effect on the esophagus. If marked malnutrition or anemia is present, appropriate drug treatment is, of course, indicated.

#### DIET

Diet plays a relatively unimportant part in the treatment of achalasia of the cardia. It is a well established fact that early in the disease an attack of dysphagia is just as likely to occur while the patient is drinking liquids as while he is partaking of solid food. In the case of advanced involvement with marked dilatation of the esophagus and retention of food, it is well to restrict the diet to liquid foods mostly until a satisfactory dilation has been accomplished. Just as soon as there is complete dilatation of the cardia, which frequently follows the first treatment, esophageal contents will pass through the cardia freely, and no further restriction in diet is necessary. After the first satisfactory treatment, all dietary restrictions should be discontinued and the patient directed to follow a regular diet of his own selection. It is surprising to see how frequently he returns in a few days with the statement that he has had very little difficulty, the obstructive symptoms having almost entirely disappeared.

#### SUMMARY

For many years the Plummer modification of the Russell cardiospasm dilator has been used, with satisfactory results. Air instead of water

may be used to distend the dilating bag, as was advised by Plummer. I believe that the success of the treatment depends entirely on complete dilation of the cardia. I do not believe that this can be accomplished by the passage of mercury-filled bougies or by the passage of bougies through an esophagoscope, owing to the fact that neither of these procedures completely dilates the lower end of the esophagus. I also believe that complete dilation can be accomplished only by an instrument with a dilating bag sufficiently large, yet not too large, to dilate the cardia completely. Of all the different types of instruments that have been devised, I believe the one best adapted for the purpose is the Plummer cardiospasm dilator. I further believe that all patients with achalasia of the cardia should be given the benefit of thorough dilation before being considered from an operative standpoint. If patients are given the benefit of thorough dilation, few will require surgical intervention.

# SURGICAL CONSIDERATIONS OF ACHALASIA

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

ALTON OCHSNER, M D

AND

MICHAEL DEBAKEY, M D

NEW ORLEANS

A variety of terms have been applied to the clinical syndrome characterized by dilatation and hypertrophy of the esophagus associated with nonorganic obstruction of the cardia. These include cardiospasm, achalasia, phrenospasm, idiopathic dilatation of the esophagus, esophagectasia, hiatal esophagismus, megaesophagus, simple ectasia of the esophagus, preventriculosis, dilatio ingluviformis oesophagi, dilatio fusi-formis and dolichoesophagus. The multifarious designations clearly reveal the controversial causation and the bewildering pathogenesis of the condition. This is further reflected by the various types of therapeutic procedures which have been employed. It is considered inopportune to attempt here a detailed discussion of the different theories and concepts of the malady, as these have been adequately reviewed in previous publications<sup>1</sup>. However, it may be desirable to present briefly some of the factors which have been considered of pathogenic significance, in order to permit a better comprehension of the varied surgical therapeutic procedures that have been employed and advocated.

Purton (1821)<sup>2</sup> is usually credited with the first description of this condition, although attention has recently been directed to a report of

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From the Department of Surgery, School of Medicine, Tulane University

1 (a) Thieding, F. Ueber Cardiospasmus, Atonie und "idiopathische" Dilatation der Speiseröhre, Beitr z klin Chir **121** 237, 1921. (b) Bull, P. N. So-Called Idiopathic Dilatation of the Esophagus, Acta chir Scandinav **58** 581, 1925. (c) So-Called Idiopathic Dilatation of the Esophagus, Ann Surg **81** 59 and 470, 1925. (d) von Hacker, V., and Lotheissen, G. Chirurgie der Speiseröhre, in von Bruns, P. Neue deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1926, vol 34. (e) Cardenal, L. La dilatacion del esofago sin estenosis organica (el llamado cardioespasmo), Cong Soc internat. de chir, Rap **1** 701, 1932. (f) Freeman, E. B. Chronic Cardiospasm. Report of Fatal Case with Pathological Findings, South M J **26** 71, 1933. (g) Sturtevant, M. Cardiospasm with a Review of the Literature, Arch Int Med **51** 714 (May) 1933. (h) Bird, C. E. Recent Advances in Surgery of the Esophagus, Surgery **6** 617, 1939. (i) Flynn, R. Achalasia of the Oesophagus, Australian & New Zealand J Surg **8** 244, 1939. (j) Sodeman, W. A. Cardiospasm or Achalasia of the Esophagus, Am J M Sc **199** 132, 1940.

2 Purton, T. An Extraordinary Case of Dilatation of the Esophagus, Forming a Sac, Extending from Two Inches Below the Pharynx to the Cardiac Orifice of the Stomach, London M & Physiol J **46** 540, 1821.

a typical case by Willis<sup>3</sup> approximately a century and a half earlier. This astute observer not only foreshadowed one of the most popular forms of present day therapy but divined its possible causation in the statement that "the mouth of the stomach being always closed, whether by a tumor or palsy, nothing could be admitted into the ventricle unless it were violently opened." This concept is, in essence, similar to that of Einhorn,<sup>4</sup> who in 1888 concluded that the cardia probably fails to open reflexly during the act of deglutition, or to that of Hurst, who subsequently coined the term "achalasia" and popularized the idea of 'absence of relaxation of the cardiac sphincter'.<sup>5</sup> Rolleston<sup>6</sup> had expressed the same opinion. Rake<sup>7</sup> and others<sup>8</sup> demonstrated degenerative changes in the ganglion cells of Auerbach's plexus at the lower end of the esophagus in cases of achalasia. On the basis of these alterations, Hurst<sup>9</sup> expressed the belief that the condition is the result of some organic change involving neuromuscular control of the sphincter. In fact, he stated the opinion that achalasia of the cardia is the "only well established example of localized disease of the autonomic nervous system." Of particular interest in this connection is the possibility of

<sup>3</sup> Willis, T, cited by Hurst<sup>9</sup>

<sup>4</sup> Einhorn, M. A Case of Dysphagia with Dilatation of the Esophagus, *M Rec.* **34** 751, 1888

<sup>5</sup> (a) Hurst, A. F., in discussion on Weber. Spasmodic Stricture of Oesophagus, *Proc. Roy Soc Med (Clin Sect.)* **7** 150 1913, (b) Case of Achalasia of the Cardia (So-Called Cardiospasm), *ibid* **8** 22, 1914, (c) Reports of Royal Society of Medicine, *Brit M J* **2** 1062, 1914, (d) Les spincters du canal alimentaire et leur signification clinique, *Arch d mal de l'app digestif* **15** 1, 1925, (e) Treatment of Achalasia of the Cardia, *Lancet* **1** 618, 1927 (f) Hurst, A. F., and Rake, G. W. Achalasia of the Cardia (So-Called Cardiospasm), *Quart J Med* **23** 491, 1930

<sup>6</sup> Rolleston, H. D. Simple Dilatation of the Oesophagus, *Tr Path Soc London* **47** 37, 1896

<sup>7</sup> Rake, G. W. A Case of Annular Muscular Hypertrophy of the Oesophagus (Achalasia of the Cardia Without Oesophageal Dilatation), *Guy's Hosp Rep* **6** 143, 1926, On the Pathology of Achalasia of the Cardia, *ibid* **7** 141, 1927

<sup>8</sup> (a) Cameron, J. A. M. Oesophagectasia in a Child, *Arch Dis Childhood* **2** 358, 1927 (b) Mosher, H. P., and McGregor, G. W. A Study of the Lower End of the Esophagus, *Ann Otol, Rhin & Laryng* **37** 12, 1928 (c) Hara, H. J. Cardiospasm, *California & West. Med.* **30** 390, 1929 (d) Beattie, W. J. H. M. Achalasia of the Cardia, *St. Barth Hosp Rep* **64** 39, 1931 (e) Scrimger, F. A. C. Idiopathic Dilatation of the Esophagus, *Ann Surg* **94** 801, 1931 (f) Etzel, E. Neuropathologia do megaesofago e megacolo. Estudo de 5 casos, *Ann Fac de med da Univ de São Paulo* **10** 383, 1934, (g) Os nervos pneumogasticos no megaesofago. Estudo anatomopatologica de 8 casos *ibid* **10** 373, 1934 (h) Lendrum, F. C. Anatomic Features of the Cardiac Orifice of the Stomach with Special Reference to Cardiospasm, *Arch Int. Med* **59** 474 (March) 1937 (i) Jares, R. M., in discussion on Gray and Skinner<sup>571</sup>

<sup>9</sup> Hurst, A. F. Some Disorders of the Esophagus, *J A M A* **102** 582 (Feb 24) 1934

a chronic vitamin B<sub>1</sub> deficiency as the cause of the degeneration of Auerbach's plexus<sup>10</sup>

In other attempts to explain the pathogenesis on the basis of a nervous mechanism the vagus nerve has been considered. Numerous investigators<sup>11</sup> have suggested a reflex irritability of the vagus nerve, which may be primary<sup>12</sup> or secondary, due to a floating kidney,<sup>13</sup> poorly masticated food<sup>14</sup> or trauma and infection<sup>15</sup>. Whereas some observers<sup>16</sup> have described degenerative lesions in the vagus nerve, others<sup>17</sup> have found no pathologic changes. As early as 1839 it was shown

10 Etzel, E. Megaesofago-megacolon y sus asociaciones morbidas, *Rev de cir de Buenos Aires* **14** 631, 1935, A avitaminose como agente etiológico do megaesofago e do megacolo, *Ann Fac de med da Univ de São Paulo* **11** 59, 1935, Megaesophagus and Its Neuropathology. A Clinical and Anatomic-Pathological Research, *Guv's Hosp Rep* **87** 158, 1937, footnotes 8 f and g

11 von Openchowsky, T. Ueber die gesammten Innervation des Magens, *Deutsche med Wchnschr* **15** 717, 1889, **23** 48, 1897. Tyson, J., Martin, E., and Evans, J. S., Jr. Diffuse Dilatation of the Esophagus Due to Cardiospasm, *New York M J* **80** 731, 1904. Smukler, M. E. Cardiospasm with Dilatation of the Esophagus, *ibid* **99** 772, 1904. Carlson, A. J., Boyd, T. E., and Percy, J. F. Studies on the Visceral Sensory Nervous System. XIV. The Reflex Control of the Cardia and Lower Esophagus in Mammals, *Arch Int Med* **30** 409 (Oct) 1922

12 Held, I. W., and Gross, M. H. Cardiospasm, *J A M A.* **66** 233 (Jan 22) 1916

13 Lockwood, C. B. Case of (So-Called) Idiopathic Dilatation of the Oesophagus, *Brit M J* **1** 1367, 1903

14 Guisez, J. De l'étiologie et pathogénie des spasmes primitifs et graves de l'œsophage, *Bull Acad de med, Paris* **83** 147, 1920, Pathogénie et traitement des grandes dilatations de l'œsophage, *Presse med* **29** 661, 1921

15 von Bergmann. Ein Fall von Dilatatio oesophagi idiopathica, *Berl klin Wchnschr* **45** 330, 1908. Meyer, H. Entstehung und Behandlung der Speiseröhrenverweiterungen und des Cardiospasmus, *Mitt a d Grenzgeb d Med u Chir* **34** 484, 1922. Stephan, cited by Fischer, W., in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 4, p 101

16 (a) Kraus, F. Die Erkrankungen der Speiseröhre, in Nothnagel, H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1902, vol 16, pt 1, sect 2, no 1, p 129. (b) Heyrovsky, H. Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre, Oesophago-gastroanastomose, *Arch f klin Chir* **100** 703, 1912-1913. (c) Pollitzer, H. Idiopathischen spindelförmigen Erweiterung des Oesophagus, *München med Wchnschr* **60** 108, 1913. (d) Loeper, M., and Forestier, J. Les lésions nerveuses du pneumogastrique et le cardiospasme récurrent dans le cancer de l'estomac, *Arch d mal d l'app digestif* **11** 307, 1921

17 (a) Rosenheim, T. Beiträge zur Oesophagoskopie, *Deutsche med Wchnschr* **24** 53 and 75, 1899. (b) Schmidt, M. B. Ueber idiopathische Oesophaguserweiterung, *ibid* **31** 1522, 1905. (c) Ewald, C. A. Idiopathische spindelförmige Erweiterung der Speiseröhre, *ibid* **33** 1036, 1907. (d) Starck, H. Zur Pathologie der Erweiterungen der Speiseröhre mit besonderer Berücksichtigung des Röntgenverfahrens, *Verhandl d deutsch Kong f inn Med* **29** 122, 1912. (e) Harbitz, F. Idiopathic Dilatation of the Esophagus. *Norsk med f legvidensk* **79** 841, 1918



experimentally in rabbits that vagal section in the neck resulted in stasis of food in the esophagus<sup>18</sup> Subsequent investigators<sup>19</sup> expressed the opinion that this was due to an increased tonus of the cardiac sphincter Some investigators<sup>20</sup> have observed that in cats as well as in dogs bilateral vagal section or destruction produced obstruction and dilatation of the esophagus, whereas others<sup>21</sup> have not In addition to the lack of uniformity of opinion concerning the vagal control of the esophagus, there are conflicting views concerning the influence of the sympathetic nervous system on the esophagus Whereas some investigators<sup>22</sup> have obtained definite response to stimulation or section of the sympathetic nerve supply, others<sup>23</sup> have not Knight,<sup>2,c</sup> who reviewed and investigated this subject, has shown that apparently some

18 Reid, J An Experimental Investigation into the Functions of the Eighth Pair of Nerves, or the Glosso-Pharyngeal, Pneumogastric, and Spinal Accessory Ednburgh M & S J **51** 269, 1839

19 Bernard Paralysis de l'œsophage par la section des deux nerfs pneumogastriques, *Compt rend Soc de biol* **1** 14, 1850 Schiff J M Leçons sur la physiologie de la digestion, Florence, Hermann Loescher, 1867 p 350 Kronecker H., and Meltzer, S Der Schluckmechanismus Seine Erregung und seine Hemmung, *Arch f Anat u Physiol*, 1883, supp, p 328 Klee P Der Einfluss der Vagusreizung auf den Abbau der Verdauungsbewegungen Röntgenversuche an der Rückenmarkskatze, *Arch f d ges Physiol* **145** 557, 1912 Ozorio de Almeida, M Sur la dilatation chronique de l'œsophage produite expérimentalement chez le chien par section partielle des pneumogastriques, *Compt rend Soc de biol* **102** 407, 1929

20 (a) Cannon, W B Esophageal Peristalsis After Bilateral Vagotomy *Am J Physiol* **19** 436, 1907 (b) Carlson, A J, Boyd, T E, and Percy J J Studies on Visceral Sensory Nervous Innervation of Cardia and Lower End of Esophagus in Mammals, *ibid.* **61** 14, 1922 (c) Kelly, U B Nervous Affections of the Esophagus, *J Laryng & Otol* **42** 221, 1927 (d) de Vasconcellos E L'œsophagogramme du chien normal et du chien porteur d'un mégacœsophage expérimental, *Compt. rend Soc de biol* **116** 1128, 1934 (e) Grondahl, J W and Haney, H F Attempt to Produce Experimentally Cardiospasm in Dogs *Proc Soc Exper Biol & Med* **44** 126, 1940

21 Krehl, L Ueber die Folgen der Vagusdurchschneidung, *Arch f Anat u Physiol*, 1892, supp, pp 278-290 Sinnhuber Beiträge zur Lehre vom muskulären Cardiaverschluss, *Ztschr f klin Med.* **50** 102, 1903 Zeller, W, and Burget, G E A Study of the Cardia, *Am J Digest Dis & Nutrition* **4** 113 1937

22 (a) Carlson, A J, and Luckhardt, A B Visceral Sensory Nervous System Vagus Control of Esophagus, *Am J Physiol* **52** 299, 1921 (b) Kurek Experimentelles Studium über die Innervation des Oesophagus *Arch f d ges Physiol* **221** 367, 1929 (c) Knight, G C The Relation of the Extrinsic Nerves to the Functional Activity of the Esophagus, *Brit J Surg* **22** 155 1934 Carlson and others<sup>20b</sup>

23 (a) Page-May, W The Innervation of the Sphincters and Musculature of the Stomach, *J Physiol* **31** 260, 1904 (b) Jurica, E J Motility of Denervated Mammalian Esophagus, *Am J Physiol* **77** 371, 1926 (c) Rieder, W Der sogenannte Cardiospasmus *Deutsche Ztschr f Chir* **217** 334 1929

of this confusion is due to the type of experimental animal employed, as the type and amount of muscle vary. Cats were employed in his experiments, because the esophagus of the cat corresponds closely to that of the human being. He demonstrated in the interdiaphragmatic and intra-abdominal portions of the esophagus an intrinsic sphincter mechanism with relaxation on stimulation of the vagus nerves and contraction on stimulation of the sympathetic nervous system. Bilateral vagotomy resulted in the clinical manifestations of achalasia, which could be prevented by sympathectomy. These findings after vagotomy were confirmed in monkeys by Ferguson<sup>24</sup>

Another concept completely antithetic to the theory of achalasia is reflected by the term cardiospasm, which was popularized by von Mikulicz,<sup>25</sup> in 1882, although Huss,<sup>26</sup> forty years previously, had propounded a similar theory. On the basis of this concept the dilatation of the esophagus is secondary to a true spasm of the cardia.<sup>27</sup> Accordingly it must be assumed that a cardiac sphincter exists. Whereas a number of observers<sup>28</sup> have maintained that such a sphincter is present, others<sup>28a</sup> have even more convincingly demonstrated its absence. It is indeed difficult to understand how such conflicting opinions can be expressed regarding an anatomic structure. But, as was pointed out by Sodeman,<sup>1</sup> equally strange is the fact that only patients with achalasia should seek out one investigator and only those with cardiospasm another

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24 Ferguson, J. H. Effects of Vagotomy on the Gastric Function of Monkeys, *Surg, Gynec & Obst* **62** 689, 1936

25 von Mikulicz, J. Ueber Gastroskopie und Oesophagoskopie, *Mitth d Ver d Aerzte in Nied Oesterreich* **8** 41, 1882

26 Huss, M. Dilatatio oesophagi ingluviformis, *Hygiea* **4** 296, 1842

27 Meltzer, S. G. Ein Fall von Dysphagie, *Berl klin Wchnschr* **25** 140, 1888

28 Cannon, W. B. The Mechanical Factors of Digestion, London, Edward Arnold & Company, 1911. Schreiber, cited by Sturtevant<sup>18</sup> Todd, T. W. The Clinical Anatomy of the Gastro-Intestinal Tract, London, Longmans, Green & Company, 1915. Bennett, T. I. The Stomach and Upper Alimentary Canal in Health and Disease, London, William Heinemann, 1925. Feldman, M., and Morrison, S. An Experimental Study of the Lower End of the Esophagus. The Effect of the Diaphragm upon the Esophagus and Cardio-Esophageal Orifice in the Normal and Bilaterally Phrenicectomized Animal, *Physiological Study, Am J Digest Dis & Nutrition* **1** 471, 1934. Thieding<sup>1a</sup> Hurst<sup>5a</sup>

28a Jackson, C. Bronchoscopy and Esophagoscopy, ed 2, Philadelphia, W. B. Saunders Company, 1927. Plenk, H. Der Magen, in von Mollendorff, W. Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol 5, pt 1. Kishi, S. Ueber die Oesophagusmuskulatur, *Arch f jap Chir* **12** 851, 1935. Fleiner, W. Neue Beiträge zur Pathologie der Speiseröhre, *München med Wchnschr* **47** 529, 1900. Zaaijer, J. H. Cardiospasm in the Aged, *Ann Surg* **77** 615, 1923. Mosher and McGregor<sup>3b</sup> Lendrum<sup>3a</sup>

Another widely held theory, originally postulated by Sauerbruch and von Hacker<sup>29</sup> and subsequently supported by others,<sup>30</sup> incriminates the diaphragm. Accordingly there is overactivity, a failure of relaxation or an incoordination of the diaphragmatic crura. Jackson<sup>30c</sup> suggested the term "phrenospasm," and others have supported this concept. Still other extraesophageal lesions have been suggested as having pathogenic significance. Handford,<sup>31</sup> in 1888, on the basis of a single observation, expressed the opinion that compression between a dilated aorta and the diaphragm may be the cause. Mosher,<sup>32</sup> who apparently conceives theories with great facility, has on various occasions suggested that the obstruction is produced by pressure on the esophagus as it passes through the hepatic tunnel or by the tips of the lungs by kinking and torsion of the redundant esophagus due to periesophageal or intramural fibrosis. Numerous other concepts have been propounded, such as "simple ectasia,"<sup>33</sup> "congenital tendency,"<sup>34</sup> trauma,<sup>35</sup> psychasthenia<sup>36</sup> and habitus<sup>37</sup>

<sup>29</sup> Sauerbruch, F., and von Hacker, R. Zur Frage des Cardiaverschluss der Speiseröhre, *Deutsche med Wchnschr* **32** 1263, 1906

<sup>30</sup> (a) Bassler, A. Cardiospasm. What Is It? What It Seems to Be, *New York State J Med* **14** 9, 1914. (b) Hill, W., in Discussion on Dilatation of Esophagus Without Anatomical Stenosis, *Proc Roy Soc Med (Sect Laryng)* **12** 33, 1919. (c) Jackson, C. The Diaphragmatic Pinchcock in So-Called "Cardiospasm," *Laryngoscope* **32** 136, 1922. (d) Caballero, R. V. Étude expérimentale de la fermeture de l'extrémité inférieure de l'œsophage, *Compt rend Soc de biol* **88** 1060, 1923. (e) Joannides, M. Influence of the Diaphragm on the Esophagus and on the Stomach, *Arch Int Med* **44** 856 (Dec) 1929. (f) Peroni, A. Considerazioni cliniche e patogenetiche su alcune discinesie dell'esofago, *Arch ital di otol* **49** 145, 1937.

<sup>31</sup> Handford, H., cited by Hurst and Rake<sup>57</sup>

<sup>32</sup> Mosher, H. P. (a) Liver Tunnel and Cardiospasm, *Laryngoscope* **32** 348, 1922, (b) Cardiospasm, *Pennsylvania M J* **26** 240, 1923, (c) The Lower End of the Esophagus at Birth and in the Adult, *J Laryng & Otol* **45** 161, 1930, (d) Fibrosis of the Terminal Portion of the Esophagus. Cardiospasm, *Proc Internat. Assemb Inter-State Post-Grad M. A. North America* **6** 95, 1931, (e) Involvement of the Esophagus in Acute and in Chronic Infection, *Arch Otolaryng* **18** 563 (Nov) 1933.

<sup>33</sup> Rosenheim<sup>17a</sup> Mosher<sup>32a</sup> b

<sup>34</sup> Zenker, F. A., in von Ziemssen, H. *Handbuch der speciellen Pathologie und Therapie*, Leipzig, F. C. W. Vogel, 1876, vol 7, pt 1 (supp.) Mackenzie, M. A. *Manual of Diseases of the Throat and Nose*, London, J. & A. Churchill, 1884, vol 1, p 117. von Luschka, H. Die spindelförmige Erweiterung der Speiseröhre, *Virchows Arch f path Anat* **42** 429 and 473, 1868. Sievers, R. Zur Kenntnis der idiopathischen Oesophagus-Erweiterung, *Ztschr f klin Med* **49** 45, 1903. Fleiner, W. Neue Beiträge zur Pathologie der Speiseröhre, *München med Wchnschr* **47** 529, 1900.

<sup>35</sup> Vinson, P. P. External Trauma as a Cause of Lesions of the Esophagus, *Am J Digest Dis & Nutrition* **3** 457, 1936. Thieding<sup>1a</sup>

It becomes obvious from this brief review of the pathogenesis that there are considerable diversity of opinion and conflict of views regarding the development of this condition. There is little wonder, therefore, that there should be such great variation in the therapeutic measures advocated and employed. In general these procedures may be classified into the conservative and the radical. In this presentation no attempt will be made to discuss the former, although it should be realized that they should always be attempted first. It is generally agreed that the radical procedures should be instituted only after the conservative measures have failed.

The various types of radical procedures which have been advocated and employed may be classified as follows:

- I Operations directed at the dilated esophagus
  - (a) Excision of wall (Jaffé, Reisinger)
  - (b) Esophagoplication (Freeman, Reisinger, Meyer)
  - (c) Esophagostomia thoracica (Zaaijer)
- II Operations directed at the cardia
  - (a) Dilatation
    - 1 Retrograde
    - 2 Transgastric (von Mikulicz)
  - (b) Plastic surgical handling
    - 1 Cardiomyotomy (Heller, Ropke)
    - 2 Cardioplasty (Marwedel, Wendel)
  - (c) Excision
    - 1 Cardiotomy (Rumpel, Pribram)
  - (d) Deviation
    - 1 Esophagogastrostomy (Heyrovsky)
- III Operations directed at the diaphragm
  - (a) Phrenotomy
  - (b) Transposition
- IV Operations directed at the nerve supply
  - (a) Vagotomy (Meyer, and Sauerbruch)
  - (b) Sympathectomy

Because of the marked dilatation of the esophagus a procedure suggesting itself as corrective would be one which would decrease the size

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36 Schindler, R. Wesen und Behandlung der Cardiospasmus, München med Wchnschr **73** 1612, 1926. Weiss, E. Personality Study in Cardiospasm. The Meaning of the Disorder from the Standpoint of Behavior, Am J Digest Dis & Nutrition **3** 1, 1936.

37 Strauss, H. Zur Diagnose und Therapie der cardiospastischen Speiseröhrenerweiterung. Berl klin Wchnschr **41** 1261 1904.

of this dilatation In 1897, Jaffe<sup>38</sup> proposed such a procedure, in which the dilated esophagus would be diminished in size by excision of long strips of its wall and closure of the defects Ten years later, Reisinger<sup>39</sup> reported a case in which this was done He exposed the esophagus through a posterior mediastinotomy opening and attempted to perform esophagoplication, but because the patient went into shock it was necessary to discontinue the operation However, at a subsequent stage several weeks later, he was able to excise several strips 2 to 3 cm in width and 15 cm in length from the esophageal wall, after which he sutured the defects Because of subsequent disruption of the esophageal wounds several operations were required before complete healing occurred However, the patient finally recovered, and the condition was improved

With a similar rationale, i e, artificial reduction in the circumference of the esophagus, Meyer,<sup>40</sup> in 1911, performed esophagoplication Using a transpleural approach through a Schede incision, he exposed the esophagus and sutured together, with interrupted silk sutures, two longitudinal folds of the esophageal wall A vagolysis was also done The patient subsequently had an esophageal fistula and died of suppurative mediastinitis Because of this, Meyer advised the use of catgut instead of silk as suture material for the esophagus In subsequent reports Meyer<sup>41</sup> reported 2 cases of similar treatment, with poor results and came to the conclusion that a plastic procedure similar to the Hemcke-Mikulicz pyloroplasty should be done Whereas these procedures attempted correction of the abnormality by an artificial reduction in the circumference of the esophagus, the rationale of the Freeman<sup>42</sup> procedure was based on diminution in length Through a cervical incision, Freeman pulled upward on the dilated esophagus until the portion below was "rendered quite taut" and then invaginated the upper segment into the lower without opening the lumen This intussusception was maintained with a few catgut sutures The patient remained improved for twenty years

38 Jaffe, K Ueber idiopathische Oesophaguserweiterung, München med Wchnschr **44** 386 1897

39 Reisinger Ueber die operative Behandlung der Erweiterung des Oesophagus Verhandl d deutsch Gesellsch f Chir **36** 86, 1907

40 Meyer, W Impermeable Cardiospasm Successfully Treated by Thoracotomy and Oesophagoplication, Ann Surg **53** 293, 1911, Impermeable Cardiospasm Successfully Treated by Thoracotomy and Esophagoplication, J A M A **56** 1437 (May 20) 1911, Thoracotomy for Impermeable Cardiospasm (Two Cases) with Remarks on Drainage After Intrathoracic Operations, Ann Surg **55** 326 1912

41 Meyer, W (a) Operative Treatment of Intractable Cardiospasm Ann Surg **26** 193, 1912 (b) in discussion on Lambert<sup>82</sup>

42 Freeman, L An Operation for Relief of Cardiospasm Associated with Dilatation and Tortuosity of the Esophagus Tr Am S A **41** 19 1923

The procedure described by Zaaier<sup>43</sup> in 1912 consisted of gastrotomy at the first stage, esophagostomy being performed subsequently, after several operations in which the esophagus was brought near the chest by preliminary thoracoplasty similar in technic to the operation he employed for cardiac carcinoma. After this, everything the patient swallowed was discharged through the fistula, collected in a bottle and subsequently emptied through the gastrostomy stoma into the stomach.

It is obvious that these procedures attacking the dilated esophagus are as irrational as repair of a hernia by diminishing the size of the sac. At present they may be considered of historical interest only. On the other hand, operative procedures directed at the cardia seem to have a more rational basis, because the obstruction to the passage of food into the stomach appears at this site. Probably because of Mikulicz' influence, the prevalent view at the turn of this century was that a true spasm of the cardiac sphincter exists in this condition. Von Mikulicz drew an analogy between this and spasm of the anal sphincter associated with a fissure. On this basis dilation appeared a rational corrective procedure, and in 1899 Lotheissen<sup>44</sup> suggested the use of "Sondierung ohne Ende," or bougienage without end. This consisted of passing a string orally through the esophagus and out of the stomach through a gastrostomy opening. Retrograde dilation could then be performed by guiding bougies along the string (fig 1). Von Hacker<sup>45</sup> reported good results from the use of this method.

In 1903, von Mikulicz<sup>46</sup> proposed and performed transgastric dilation of the cardia. Through a laparotomy incision he exposed the stomach and introduced an instrument resembling a glove stretcher through an incision into the anterior gastric wall and into the cardia. "The dilatation was gradually affected to such an extent that the (rubber covered) blades of the instrument were about 7 cm apart." After this he was able to introduce his second and third fingers through the cardia very readily (fig 2). After this, over a three month period of observation, the "patient was able to swallow every kind of food without any difficulty." According to Lusena<sup>47</sup> this procedure was performed by Loreta<sup>48</sup> as early as 1884.

43 Zaaier, J. H. Oesophagotomia thoracalis, Beitr. z. klin. Chir. **77** 497, 1912.

44 Lotheissen, cited by von Hacker and Lotheissen<sup>14</sup>.

45 von Hacker, in discussion on Reisinger<sup>39</sup>.

46 von Mikulicz, J. Small Contributions to the Surgery of the Intestinal Tract. Boston M. & S. J. **148** 608, 1903; Zur Pathologie und Therapie des Cardiospasmus, Deutsche med. Wchnschr. **30** 50, 1904; Zur Pathologie und Therapie des Cardiospasmus, *ibid.* **30** 17, 1904.

47 Lusena, G. La chirurgia dell'esofago, Cong. Soc. internat. de chir., Rap. **1** 641, 1932.

48 Loreta, cited by Lusena<sup>47</sup>.

In order to obviate opening of the stomach and possible peritoneal contamination, Rotgans<sup>49</sup> and subsequently others<sup>50</sup> performed dilation of the cardia with the fingers by forcefully invaginating the anterior wall of the stomach up through the cardia. Judd, Vinson and Greenlee<sup>51</sup> suggested the use of a previously swallowed thread as a guide to the cardia when the stomach was opened. Anschütz<sup>52</sup> dilated the cardia with a balloon but opened the abdomen in order to control more accurately the location of the balloon. Von Mikulicz proposed his procedure on the basis that it would permit more accurate control of the dilation

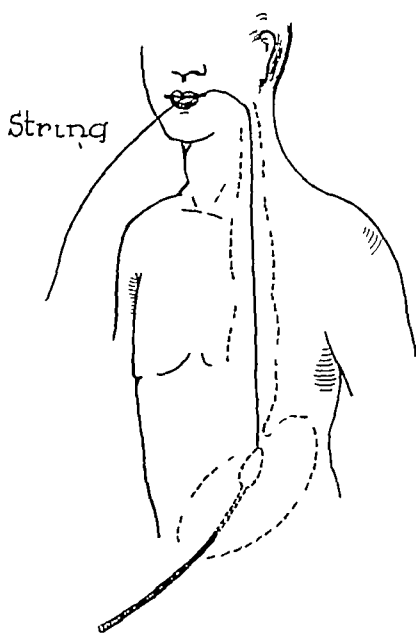


Fig 1—Diagrammatic illustration of retrograde dilation in the treatment of achalasia. The bougie is guided along a string introduced orally through the esophagus and out of the stomach through a gastrostomy.

<sup>49</sup> Rotgans, cited by Zaaijer<sup>43</sup>

<sup>50</sup> (a) Wakeley, C P G. A Case of Hiatal Oesophagismus in a Man Aged Thirty Six Years, *Brit M J* **1** 589, 1916. (b) Schäfer. Operativer Behandlung des Kardiospasmus, *Zentralbl f Chir* **47** 230, 1920. (c) Kümmell, H. Zur Operation des Kardiospasmus und des Oesophaguscarcinoms, *Arch f klin Chir* **117** 193, 1921. (d) Zur Operation des Kardiospasmus und des Oesophaguscarcinoms, *Verhandl d deutsch Gesellsch f Chir* **45** 327, 1921. (e) Gould G A. Dysphagia for Forty-One Years, *New England J Med* **209** 962, 1933 Thieding<sup>1a</sup>

<sup>51</sup> Judd, E S, Vinson, P, and Greenlee, D P. Retrograde Dilatation of the Oesophagus for Cardiospasm, *Surg, Gynec & Obst* **48** 494, 1929

<sup>52</sup> Anschütz, in discussion on Kümmell,<sup>50d</sup> *Verhandl d deutsch Gesellsch f Chir* **45** 147, 1921

and therefore would be less hazardous than blind dilation from above. However, in 1903 he stated that an instrument might be devised to accomplish this result which could be introduced orally. Apparently he was not familiar with Russell's<sup>53</sup> publication. It is obvious that von Mikulicz' procedure accomplishes little more than dilation by the natural oral route and is no less dangerous. Cases have been reported in which the procedure was followed by marked hemorrhage,<sup>54</sup> fatal rupture, mediastinitis<sup>55</sup> and periesophageal abscess<sup>56</sup>. Of the 80 cases

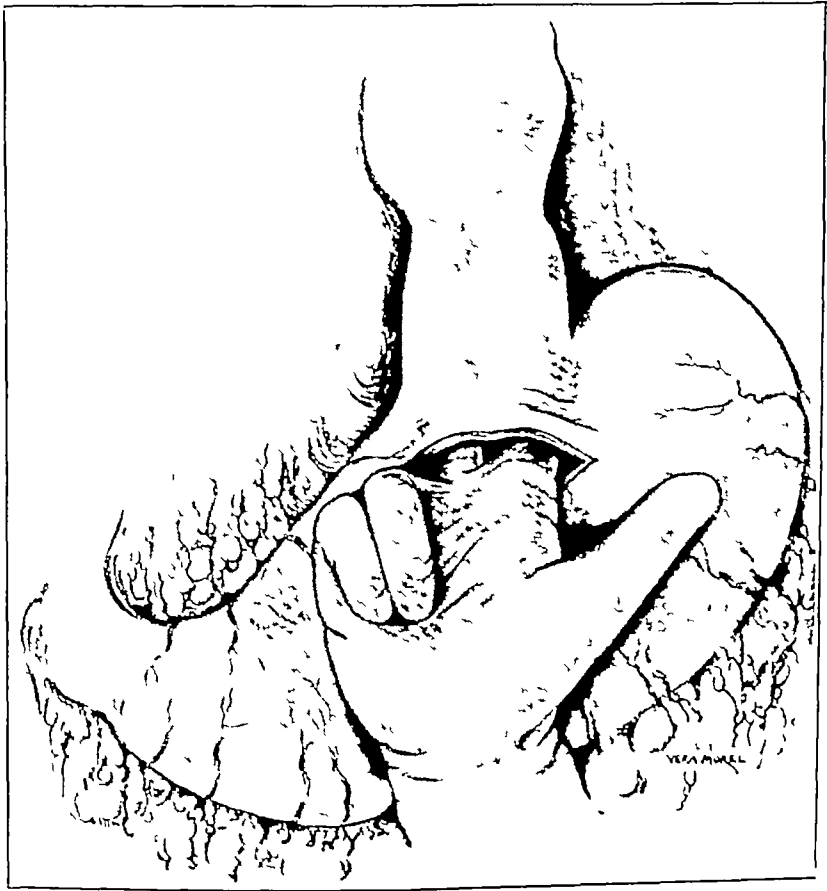


Fig 2—Drawing illustrating transgastric dilation of the cardia in the treatment of achalasia

53 Russell, J. C. Diagnosis and Treatment of Spasmodic Stricture of the Oesophagus, *Brit M J* 1 1450, 1893

54 Galpern, Y. Kardiospasmus, Dilatation nach Mikulicz, profuse Blutung, *Zentralbl f Chir* 57 87, 1930

55 Schmilinsky, in discussion on Schäfer<sup>50b</sup>

56 Gottstein, G. Die operative Behandlung Cardiospasmus, *Zentralbl f Chir* 31 1362, 1904



collected from the literature,<sup>71</sup> the patients in 7 (89 per cent) died and

- 57 (a) Gottstein, G Ueber die chirurgische Behandlung des Kardiospasmus Deutsche med Wchnschr **30** 1597, 1904, (b) Weitere Fortschritte in der Therapie des chronischen Cardiospasmus, Arch f klin Chir **87** 497, 1908 (c) I edderhose Cardiospasmus, Deutsche med Wchnschr **30** 1669, 1904, (d) in discussion on Gottstein<sup>76</sup> (e) Goldmann Kardiospasmus, Munchen med Wchnschr **52** 1416 1905 (f) Wilms Fall von Kardiospasmus mit retrograder Dilatation behandelt ibid. **52** 144, 1905 (g) von Bonsdorff, H Contribution to the Question of the Operative Treatment of Cardiospasm, Finska lak-sallsk handl **58** 305, 1906 Nord tidskr f terapi **4** 97, 1906 (h) Brünnig, F Ein Beitrag zur Lehre vom Cardiospasmus, Beitr z klin Chir **48** 228, 1906 (i) Erdmann Cardiospasm with Report of an Operative Case, Ann Surg **43** 224, 1906 (j) Plummer, H S Cardiospasm, with Report of Cases, J Minnesota M A **26** 419, 1906 (l) von Eiselsberg, A Presentation of Case Before the Medical Society of Vienna June 21, 1907, Wien klin Wchnschr **20** 811, 1907 (l) Graff Cardiospasmus Deutsche med Wchnschr **33** 447, 1907, (m) in discussion on Reisinger<sup>70</sup> (n) Kramer-Petersen On Cardiospasm, Ugesk f læger **52** 1401, 1908 (o) Noroth, cited by von Hacker and Lotheissen<sup>14</sup> (p) Iden, J H Cardiospasm Report of a Case, Treatment by Operation and Subsequent Dilatation J A M A **56** 1438 (May 20) 1911 (q) Bowker, G E Discussion of a Note on Cardiospasm, Brit. M J **2** 917, 1913 (r) Albu Beitrag zur Lehre von der idiopathischen Oesophagusdilatation, München med Wchnschr **64** 749, 1917 (s) Schloffer Cardiospasmus, Wien klin Wchnschr **31** 88, 1918 (t) Pamperl R Zur operativen Behandlung des Kardiospasmus, Deutsche Ztschr f Chir **148** 206, 1919 (u) Clairmont, P, in discussion on Kümmell, <sup>74</sup> Verhandl d deutsch Gesellsch f Chir **45** 142, 1921 (v) Urrutia, L, cited by von Hacker and Lotheissen<sup>14</sup> (w) Watts, S H Cardioplasty for Cardiospasm, Tr Am S A **41** 25 1923 (x) Tuffier Dilatation de l'oesophage Mega-oesophage Operation Resultat fonctionnel suivi sur radiographie, huit mois apres, Bull et mem Soc de chir de Paris **48** 446, 1922 (y) Crone-Munzebrock, E Die operative Behandlung des echten Kardiospasmus, Zentralbl f Chir **53** 2386, 1926 (z) Doberer, cited by von Hacker and Lotheissen<sup>14</sup> (a') Walton, A J The Surgical Treatment of Cardiospasm, Brit. J Surg **12** 701, 1925 (b') Enderlen, in discussion on Fromme,<sup>77</sup> Arch f klin Chir **157** 138, 1929 (c') Hesse, E Ueber chirurgische Eingriffe an der Cardia und am Bauchabschnitt der Speiseröhre bei gutartigen Erkrankungen, Deutsche Ztschr f Chir **213** 23, 1929 (d') Larget, M, and Lamare, J P Cardiospasme ou retrecissement oesophagien, dilatation forcee du cardia par voie transgastrique, resultats eloignes de deux cas, Bull et mem Soc nat. de chir **55** 886, 1929 (e') Maconie, A C Cardiospasm Treated Successfully by Operation, Brit M J **1** 398, 1929 (f') Adams, A W Thoracic Stomachs A Study of Pharyngeal Pouch and Cardiospasm, with Report of Three Cases, ibid **2** 208, 1930 (g') Lamson, O F Surgical Treatment of Cardiospasm, Northwest Med **29** 125, 1930 (h') Butler H B A Case of Achalasia of the Cardia, Brit M J **2** 565, 1931 (i') Jirasek A Un cas d'oesophago gastro-anastomose reussie, Bull et mem Soc nat de chir **57** 1189 1931 (j') Rieder, W Die Therapie des sogenannten Kardiospasmus, Beitr z klin. Chir **151** 495, 1931 (k') Khodkov, V M Surgical Therapy in Connection with Three Cases of Cardiospasm, Sovet khir **9** 447, 1936 (l) Grav H K, and Skinner, I C The Operative Treatment of Cardiospasm J Thoracic Surg to be published (m') von Mikulicz<sup>40</sup> (n') Lusena<sup>47</sup> (o') Lorica<sup>4</sup> (p)

the operations in 8 (101 per cent) were failures. Good results were reported in 56 (70.8 per cent) and improvement in 6, and the results were unknown in 2.

The next type of surgical procedure directed at the cardia was plastic. With a rationale similar to that of the Ramstedt<sup>58</sup> procedure for hypertrophic pyloric stenosis, Heller,<sup>59</sup> in 1913, performed an extramucous cardiomyotomy which had been proposed by Gottstein<sup>60</sup> in 1901. This

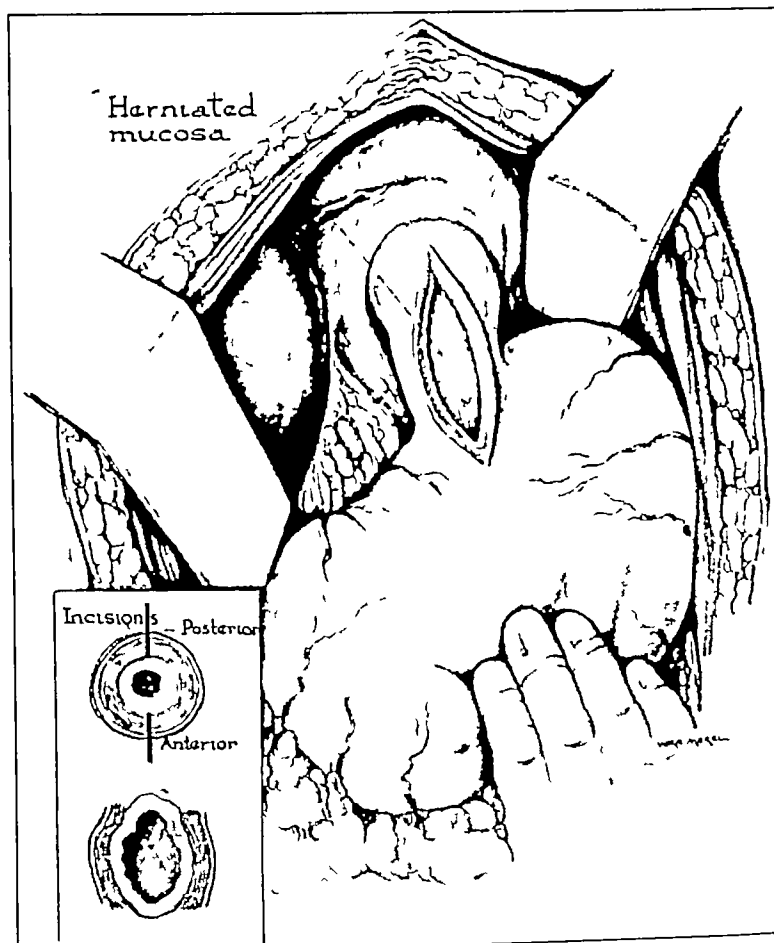


Fig 3—Extramucous cardiomyotomy in the treatment of achalasia. The musculature of the cardiac end of the esophagus is incised longitudinally down to the mucosa for about 8 to 10 cm. As is shown in the inset, the vertical incisions are made anteriorly and posteriorly.

Rotgans<sup>49</sup> (*q'*) Footnote 50 (*r'*) Judd and others<sup>51</sup> (*s'*) Anschütz<sup>52</sup> (*t'*) Russell<sup>53</sup> (*u'*) Galpern<sup>54</sup> (*v'*) Schmilinsky<sup>55</sup> (*w'*) Gottstein<sup>60</sup>

58 Ramstedt, C. Zur Operation der angeborenen Pylorusstenose, *Monatschr f Kinderh* 11 409, 1912.

59 Heller, E. Extramuköse Cardiaplastik beim chronischen Cardiospasmus mit Dilatation des Oesophagus, *Mitt a d Grenzgeb d Med u Chir* 27 141, 1913-1914.

60 Gottstein, G. Technik und Klinik der Oesophagoskopie, *Mitt a d Grenzgeb d Med u Chir* 8 57, 511 and 99, 1901.

operation consisted of exposure of the stomach and the cardia through a laparotomy incision, mobilization of the cardia and esophagus for 8 to 10 cm and longitudinal incision of the musculature of the cardiac end of the esophagus down to the mucosa (fig 3). A vertical incision approximately 8 cm long was made anteriorly and a similar one posteriorly. Heller<sup>61</sup> insisted on the necessity of two incisions because of the probably continued function of the sphincter due to bridging of the defect by scar if a single incision were made. However, Zaaier<sup>62</sup> and de Brüne Groeneveldt<sup>63</sup> stated that one incision is sufficient. As usual, this procedure was subsequently modified by a number of surgeons. In 1914, Röpke<sup>64</sup> suggested incising the hiatus to permit better mobilization and removing the periesophageal tissues down to the mucosa for a distance of 6 cm. Schaldemose<sup>65</sup> preferred making a circular incision over a grooved director inserted through a small opening down to the mucosa and then up between the mucosa and the muscle layer. Similarly, Oliveira Mattos<sup>66</sup> suggested that a forceps be used to dissect between the mucosa and the muscle layer before the operator incises the latter and resects a part of it. These modifications have the obvious purpose of avoiding opening the lumen by accidentally tearing or incising the mucosa. That this is not merely a theoretic objection is shown by the fact that of 104 collected cases,<sup>67</sup> accidental tearing of the mucosa

61 Heller, in (a) discussion on Röpke,<sup>64a</sup> (b) in discussion on Kummell,<sup>60a</sup> *Verhandl. d. deutsch. Gesellsch. f. Chir.* **45** 144, 1921, (c) *Die Behandlung des Kardiospasmus*, *Med. Welt* **6** 1675, 1932.

62 Zaaier, J. H. *Cardiospasm in the Aged*, *Ann. Surg.* **77** 615, 1923.

63 de Brüne Groeneveldt, J. R. *On Cardiospasm*, *Nederl. tijdschr. v. geneesk.* **2** 1281, 1918.

64 Röpke (a) *Zur Operation des Oesophagospasmus*, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **43** 121, 1914, (b) in discussion on Kummell,<sup>60a</sup> *ibid.* **45** 146, 1921, (c) in discussion on Fromme,<sup>67w</sup> *Arch. f. klin. Chir.* **157** 136, 1929.

65 Schaldemose, V. *Operated Cases of Idiopathic Dilatation of the Esophagus*, *Nord. kir. för. förhandl.* **11** 231, 1916.

66 Oliveira Mattos, J. *Tratamento megaesofago (acalasia do cardia) pela esfincterectomia cardica*, *Rev. Assoc. paulista de med.* **13** 217, 1938.

67 (a) Ambrumjanz *Ueber einer Modification der Hüllerschen Operation beim Kardiospasmus*, *Zentralorg. f. d. ges. Chir. u. Grenzgeb.* **50** 747, 1930 (b) Soupault, R., and Hamburger, M. *Retrecissement oesophagocardiaque dit essentiel opere et gueri*, *Arch. d. mal. de l'app. digestif* **22** 48, 1932, (c) *Resultat eloigne d'une oesophago-cardiotomie pour retrecissement oesophagien*, *ibid.* **23** 103, 1933, (d) *Les résultats éloignés de l'opération de l'oesophago-cardiotomie extra-muqueuse*, *ibid.* **26** 942, 1936 (e) Borchgrevink, O., in discussion on Schaldemose,<sup>65</sup> (f) in discussion on Kummell,<sup>60a</sup> *Verhandl. d. deutsch. Gesellsch. f. Chir.* **45** 148, 1921 (g) Exalt, O. J. *A Case of Chronic Cardiospasm*, *Nederl. tijdschr. v. geneesk.* **2** 1276, 1918 (h) Lindstrom, T. E. *A Case of Cardiospasm with Dilatation of the Esophagus*, *Hygiea* **80** 1169, 1918 (i) Noordenbos W. *Cardiospasmus*, *Nederl. tijdschr. v. geneesk.* **2** 1278, 1918 (j) Zaaier, J. H.

occurred in 14, and in 2 of these the patients died of consequent infection. There were a third death, due to perforation following bougienage after the completion of the operation, and a fourth, due to pulmonary embolism, giving a mortality rate of 4 per cent. Recurrence took place in 14 cases of the collected group. The results were considered good in 80 and improvement was observed in 6 others.

Kardiospasm und Esophagusaffection, Thesis, Leyden, 1918, abstracted Zentralbl f Chir **46** 57, 1919, (k) On Surgery of the Oesophagus, Cong Soc internat de chir, Rap **1** 485, 1932 (l) Mintz, W. Operative Eingriffe bei Kardiospasmus und Megaeosophagie, Deutsche med Wchnschr **46** 1296, 1920 (m) Enderlen, in discussion on Kummell,<sup>10d</sup> Verhandl d deutsch Gesellsch f Chir **45** 147, 1921 (n) Payr, E, cited by Heller,<sup>101b</sup> (o) in discussion on Kummell,<sup>100d</sup> ibid **45** 147, 1921, (p) Chirurgische Behandlung des Kardiospasmus, Zentralbl f Chir **56** 3103, 1929 (q) König, cited by von Hacker and Lotheissen<sup>1d</sup> (r) Horhammer, C. Das Einmanschettierungsverfahren nach Goepel an den kardialen Magenpartien, mit besonderer Berücksichtigung Einpflanzung des Oesophagus, Zentralbl f Chir **50** 633, 1923 (s) Hurst, A. F., and Rowlands, R. P. Case of Achalasia of Cardia Relieved by Operation, Proc Roy Soc Med (Clin Sect) **17** 45, 1924 (t) Reise Kardiospasmus, Zentralbl f Chir **51** 2137, 1924 (u) Camargo, A. C., Vampre, E., and Parisi, R. Mal de engasgo, cura pela operação de Heller, 2 observação, Bol Soc de med e cir de São Paulo **7** 54, 1924-1925 (v) Chaves, J. A. Therapeutica cirurgica do mal de engasgo, Brasil-med **41** 43, 1927 (w) Fromme, A. Erfahrungen mit der Operation des Kardiospasmus, Arch f klin Chir **157** 606, 1929 (x) Delbet, P. Megaeosophage Operation par voie abdominale, Bull et mem Soc nat de chir **55** 481, 1929, (y) Troisième cas de cardiospasmie opere par voie abdominale, ibid **57** 586 and 1056, 1931, (z) Retrecissement simple de l'oesophage (cardiospasmie) opere par la voie abdominale, ibid **57** 1057, 1931 (a') Oberthür, H. Traitement chirurgical de la dilatation dite idiopathique de l'oesophage, Arch d mal d l'app digestif **21** 649, 1931 (b') Jacobovici, I., and Hanganut. La cardio-myotomie dans le traitement de la dilatation idiopathique de l'oesophage, Romania med **9** 325, 1931 (c') Turner, G. G. Some Experiences in the Surgery of the Esophagus, New England J Med **205** 657, 1931, (d') Personal Experience in the Surgery of the Lower Esophagus, Cong Soc internat de chir, Rap **1** 725, 1932 (e') Charbonnel and Masse. Le traitement chirurgical du megaeosophage. L'oesophago-cardiomyotomie extramuqueuse (Un cas personnel), Bordeaux chir **3** 213, 1932, (f') Méga-oesophage avec retrecissement inferieur, operation par voie abdominale (cardiooesophagotomie extramuqueuse) Resultat datant de sept mois, Bull et mem Soc nat de chir **58** 1092, 1932 (g') Charbonnel, in discussion on Chenut<sup>100e</sup> (h') Jauregui, P., and Subiza, V. Cardioespasmo operado por via abdominal. Curacion, Bol y trab, Soc de cir de Buenos Aires **16** 1525, 1932 (i') Soupault, R. L'oesophago-cardiotomie dans les retrecissements simples de l'oesophage inferieur, Cong Soc internat de chir, Rap **1** 759, 1932, (j') L'oesophago-cardiotomie extra-muqueuse (operation de Heller), J de chir **41** 727, 1933, (k') Les retrecissements cardio-oesophagiens (ex-cardiospasmes), Médecine **15** 889, 1934 (l') Hartung, in discussion on Fromme<sup>101g</sup> (m') Recalde, J. F. Cardiospasm, disfagia y mega-esofago, simpaticectomia esofágica, estadística quirurgica, Semana med **1** 1552, 1933 (n') Vampre, E. Le "mal de engasgo" et son traitement chirurgical, Rev sud-am de med et de chir **4** 493, 1933 (o') Carayannopoulos, A. Sur un cas

The other plastic operation on the cardia is analogous to the Heinecke-Mikulicz pyloroplasty<sup>68</sup> This was first performed by Wendel,<sup>69</sup>

- de mégæsoophage, Bull et mem Soc nat de chir **60** 14, 1934 (*p'*) Fruchaud, H Un cas de retrecissement cardio-œsophagien essentiel traite par operation de Heller *ibid.* **60** 1264, 1934 (*q'*) Jauve Stenose cardio-œsophagienne chez l'enfant Operation de Heller, Lyon chir **31** 586, 1934 (*r'*) Leriche, R in discussion on Jauve.<sup>67q'</sup> (*s'*) Rohde, C Zur Operation des Kardiospasmus, Zentralbl f Chir **61** 977, 1934 (*t'*) Buzoianu, G, and Ionescu, D Cardiomyotomy in Esophageal Cardiospasm, Rev de chir, Bucureşti **38** 137, 1935 (*u'*) Diez, J Cardioesopasmo y operacion de Heyrovsky, Bol y trab, Soc de cir de Buenos Aires **19** 924 1935 (*v'*) Cardioesopasmo y operacion de Heller, *ibid.* **19** 846, 1935, (*w'*) El tratamiento quirurgico del cardioesopasmo (operaciones de Heller y de Heyrovsky), Prensa med. argent **23** 155, 1936 (*x'*) Lotheissen, G Kardiendyse, die neue Operation zur Behandlung des Kardiospasmus, Zentralbl f Chir **62** 2658, 1935 (*y'*) Baumgartner, in discussion on Magnant.<sup>67b''</sup> (*z'*) Hainant, A, and Chalnot Deux cas de megaœsophages traites par la technique de Heller, Rev med de Nancy **64** 294 1936 (*a''*) Kuss, G A propos des retrecissements cardio œsophagiens Mem Acad. de chir **62** 838, 1936 (*b''*) Magnant, J S Retrecissement cardio-œsophagien Intervention par voie abdominale Resultat eloigne, *ibid.* **62** 761, 1936 (*c''*) Marinacci, S Esofago-cardiotomia extramucosa (operazione di Heller), Arch ital di chir **44** 698, 1936 (*d''*) Most, in discussion on Frey.<sup>80b</sup> Arch f klin. Chir **186** 19, 1936 (*e''*) Pieri, G Sulla cura chirurgica del cardiospasm, Riforma med **52** 1051, 1936 (*f''*) Desplas, B, and Aime, P Deux cas de stenosis hypertrophique du cardia, Mem Acad de chir **62** 843 1936 (*g''*) Desplas, B, Durand, G, and Aime, P Megaœsophage par stenose sus-cardiaque, cravate musculaire et cercle vasculaire anormal stenasant Intervention Guérison Resultats radiographiques, Arch d mal de l'app digestif **27** 877, 1937 (*h''*) Abbeloos Observation nouvelle de cardiospasm avec megaœsophage guerri par operation de Heller, J de chir et ann Soc belge de chir **36-34** 631 1937 (*i''*) Girard, L, and Ranjard, C Phreno-cardiospasm et cardiotomie, Oto-rhino-laryng internat **21** 132, 1937 (*j''*) Vasconcelos, E, and Botelho G Cirurgia do megaesofago, São Paulo, Companhia Editora Nacional 1937 (*k''*) Huard, P, and Long, M Deux cas de retrecissement cardio-œsophagien traites par l'operation de Heller, Rev med franç d'Extreme-Orient **16** 31, 1938 (*l''*) Rousseaux Cardiospasm chronique Operation de Heller Resultat eloigne Rev med de Nancy **67** 28, 1939 (*m''*) Christide, E Mega-œsophage opere par le procede de "Heller" et guerri, Lyon chir **36** 690, 1940 (*n''*) Ferrari R C, and Perez Zabala, M La operación de Heller en el tratamiento de los fenomenos de estenosis benignos al nivel del cardias, Bol Inst. de clin. quir **12** 64 1936 (*o''*) La operacion de Heller en el tratamiento del llamado cardiospasm, Semana med. **1** 1905, 1936 (*p''*) Perez Zabala, M, and Ferrari, R C La operacion de Heller en el tratamiento de los fenomenos de estenosis benignos al nivel del cardias Bol y trab, Soc. de cir de Buenos Aires **20** 176, 1936 (*q''*) Scrimger<sup>80e</sup> (*r''*) Clairmont<sup>80u</sup> (*s''*) Jirasek<sup>87i'</sup> (*t''*) Heller<sup>80</sup> (*u''*) Heller<sup>81</sup> (*v''*) Zaaijer<sup>80-w''</sup> de Brune Groeneveldt<sup>83</sup> (*x''*) Ropke<sup>84</sup> (*y''*) Schaldemose<sup>85</sup>
- 68 Frömmler, F Operation der Pylorusstenose, Inaug Dissert Fürth, A Schröder, 1886 von Mikulicz, J Zur operativen Behandlung des stenierenden Magengeschwürs, Arch f klin Chir **37** 79, 1888
- 69 Wendel, W Zur Chirurgie des Oesophagus, Arch f klin Chir **93** 311 1910

in 1910, although it had been suggested by Marwedel<sup>70</sup> seven years previously. The procedure consists of making a longitudinal incision through the entire wall of the cardia and suturing the defect transversely, thus increasing the diameter of the lumen at this site (fig 4). In the United States, Meyer,<sup>71b</sup> in 1913, successfully performed this operation through a transpleural approach. Since then there have been 20 cases<sup>71</sup> reported, with 1 death<sup>71b</sup>. Good results were obtained in

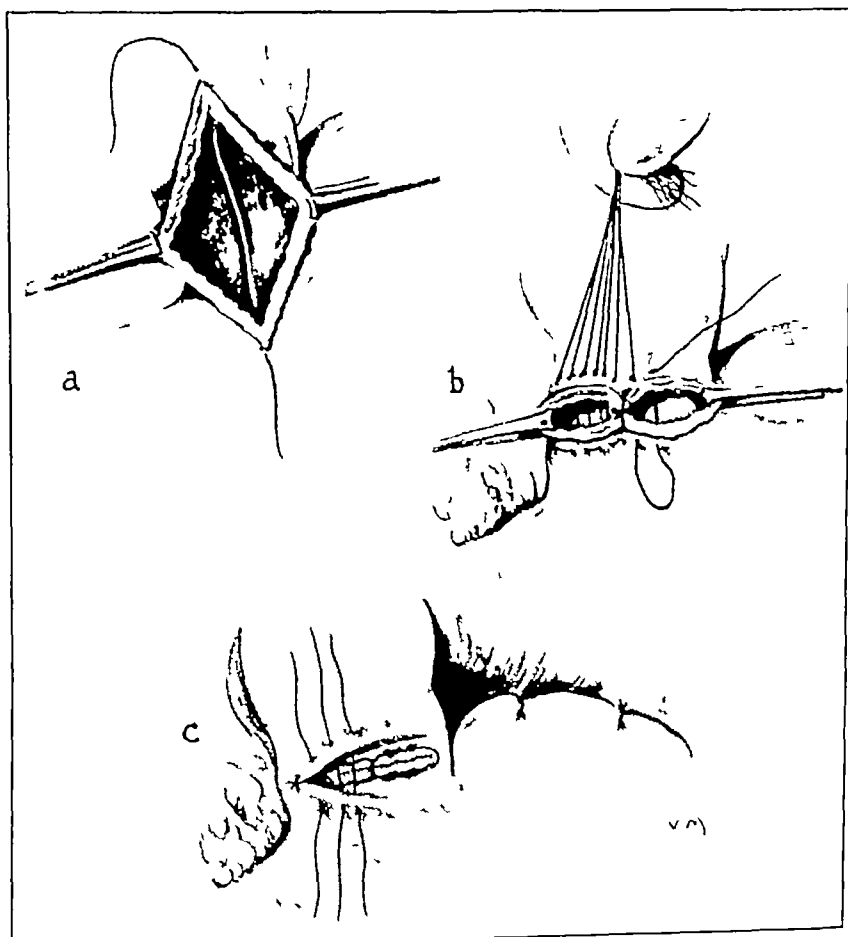


Fig 4—Cardioplasty in the treatment of achalasia. A longitudinal incision is made (a) through the entire wall of the cardia, and the defect is sutured transversely (b and c).

70 Marwedel, G. Die Aufklappung des Rippenbogens zur Erleichterung operativer Eingriffe im Hypochondrium und im Zwerchfellkuppelraum, *Zentralbl f Chir* 30 938, 1903.

71 (a) Lecene, P. Stenose inflammatoire avec spasme du cardia, dilatation œsophagienne considérable. Cardioplastie. Guérison, *Bull et mem Soc de chir de Paris* 45 710, 1919, (b) in discussion on Larget and Lamare<sup>57d</sup>, (c) Sencert, L., and Simon, R. Le traitement opératoire de la dilatation idiopathique de

all except 1 case This was reported by Bull,<sup>1b</sup> who apparently intended to perform the operation of Heller but, because the mucosa was accidentally torn, sutured the defect transversely The patient had a recurrence, and an esophagogastrostomy was subsequently done A modification of this procedure, analogous to the Fredet-Weber type of pyloroplasty,<sup>72</sup> was proposed by Girard<sup>73</sup> in 1915 In order to obviate opening the lumen and thus avoid possible peritoneal contamination, Girard performed the operation by making a longitudinal incision down to the mucosa and then suturing the resultant defect transversely (fig 5) He reported 2 cases with successful results In 1933, Ohsawa<sup>74</sup> reported 6 cases in which operation was similarly performed through an approach designated as a free transdiaphragmatic thoracolaparotomy, with good results in all We have been able to collect 14 cases<sup>75</sup> in which the

l'œsophage, Rev de chir de Paris **59** 355, 1921 (d) Gregoire, R Voie d'accès sur le segment cardio-œsophage permettant d'éviter la plevre et le peritoine, J de chir **21** 673, 1923, (e) Methode permettant d'attendre le segment cardio-œsophage en évitant la plevre et le peritoine, Bull et mem Soc de chir de Paris **49** 600, 1923, (f) Resultat au bout d'un an d'une intervention pour dilatation idiopathique de l'œsophage Section du diaphragme par voie thoraco abdominale extra-sereuse (Esophago-gastroplastie, Bull et mem Soc nat de chir **49** 1322, 1923, (g) A propos de la dilatation idiopathique de l'œsophage, ibid **49** 1502, 1923, (h) Pathogenie et traitement de la dilatation idiopathique de l'œsophage, Arch d mal de l'app digestif **14** 455, 1924, (i) Phrenospasme (Esophago-gastroplastie par voie thoraco-abdominale extra-sereuse, Bull et mem Soc nat de chir **52** 757, 1926, (j) Etat actuel de la chirurgie de l'œsophage, Cong Soc internat de chir, Rap **1** 219, 1932 (k) Lagas, F M, cited by Charbonnel and Masse<sup>67f</sup> (l) Wendel in discussion on Rieder<sup>57j</sup> (m) Graham, R, cited by Janes<sup>81</sup> (n) Murray, G, cited by Janes<sup>81</sup> (o) Bull<sup>1b</sup> (p) Janes<sup>81</sup> (q) Footnotes 57 c' and k' (r) Footnotes 67 u and k'

72 Fredet La stenose hypertrophique du pylore chez le nouveau-ne, Arch d mal de l'app digestif **2** 393, 1908 Weber, W Ueber eine technische Neuerung bei der Operation der Pylorus-Stenose des Säuglings, Berl klin Wchnschr **47** 763, 1910

73 Girard, cited by von Hacker and Lotheissen<sup>1d</sup>

74 Ohsawa, T The Surgery of the Esophagus, Arch f jap Chir **10** 605, 1933

75 (a) Bard, L Le megaoesophage, cas particulier des dilatations idiopathiques des organes cavitaires, Arch d mal de l'app digestif **9** 541, 1918, (b) Note complementaire sur le megaoesophage, ibid **10** 116, 1919 (c) Hertz, J, and Braine, J Phreno-spasme Elargissement de l'orifice diaphragmatique de l'œsophage. Esophagoplastie par voie thoraco-abdominale extrasereuse, Bull et mem Soc nat de chir **50** 569, 1924 (d) Braine, J Accès de l'œsophage mediastinal inferieur et du cardia par la voie thoraco-abdominale posterieure sous pleuro-peritoneale spécialement dans les dilatations "idiopathiques" de l'œsophage, megaoesophages et phrénospasmes, Cong Soc internat de chir, Rap **1** 763, 1932 (e) Lorenzo, R, and Boto, D Megaesofago de larga data, exito quirurgico, Prensa med argent **24** 349, 1937 (f) Fromme<sup>67w</sup> (g) Girard<sup>72</sup> (h) Ohsawa,<sup>74</sup>

extramucous cardioplasty was done. There were no deaths, and good results were obtained in all. Thus, in 36 cases in which cardioplasty was done there was only 1 death, and only 1 recurrence was reported. Good results were obtained in 93.1 per cent of cases. Such impressive results would not be expected to follow a procedure which obviously increased the diameter of the cardia relatively little.

Excision of the cardia followed by esophagogastrostomy was originally proposed by Rumpel<sup>76</sup> in 1897 and was performed by Bier in 1920.

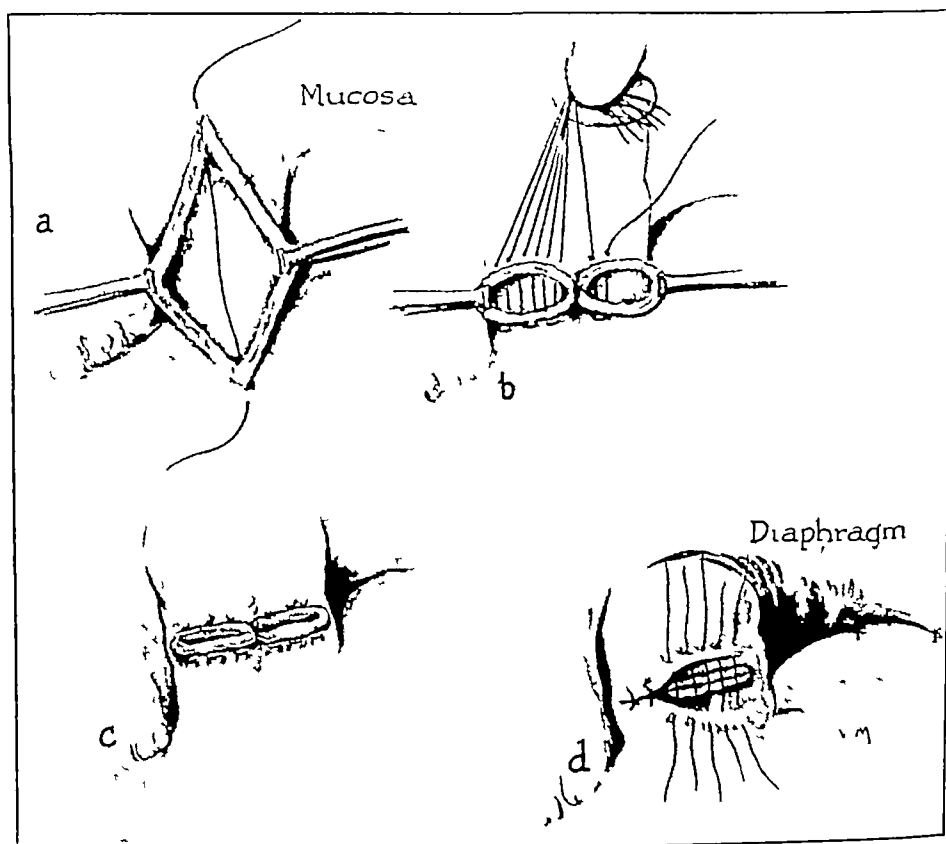


Fig 5—Extramucous cardioplasty in the treatment of achalasia. A longitudinal incision is made through the musculature of the cardiac end of the esophagus down to the mucosa, and the defect is sutured transversely.

Bier's case was reported by Pribram,<sup>77</sup> who did not consider the condition typical of cardiospasm, because there was no hypertrophy at the

76 Rumpel, T. Die klinische Diagnose der spindelförmigen Speiseröhrenverweiterung, München med Wchnschr **44** 383, 1897.

77 Pribram, B. O. Zur Pathologie und Chirurgie der spastischen Neurosen, Arch f klin chir **120** 207 1920, in discussion on Kummell,<sup>50a</sup> Verhandl d deutsch Gesellsch f Chir **45** 147, 1921.



lower end of the esophagus and the cardia was wide open. However, the clinical manifestations were characteristic of cardiospasm. The patient died of cardiac failure the day following the operation. A second case, in which treatment was successful, was reported more recently by Radlinski<sup>78</sup>. The fact that these are the only 2 cases that have been reported emphasizes the objectionable features of the opera-

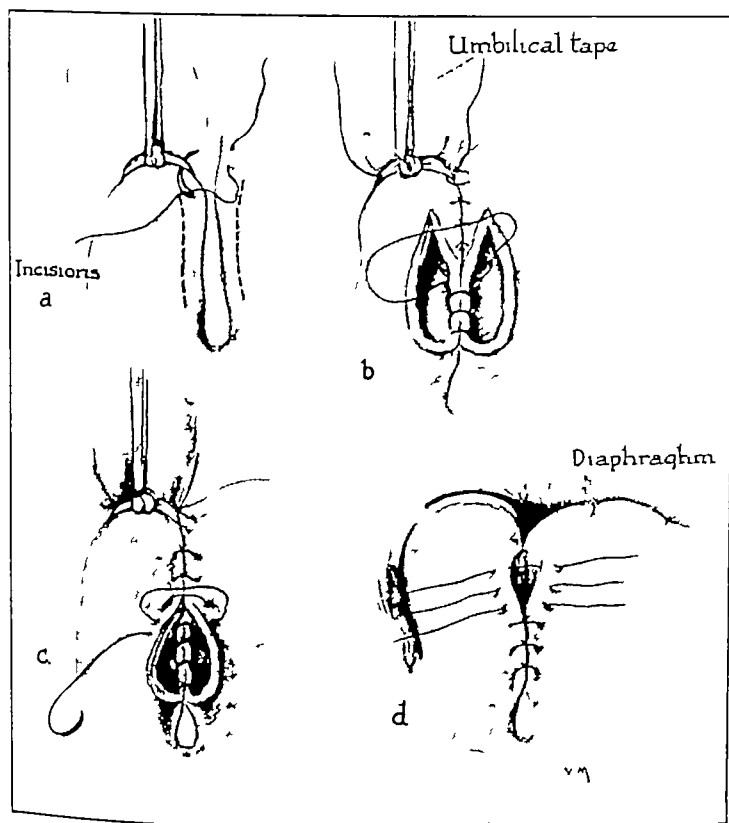


Fig 6—Technic of side to side esophagogastrostomy as originally done by Heyrovsky in the treatment of achalasia. A new opening is made between the esophagus and the stomach, thus short-circuiting the cardiac orifice.

tion. Such a radical procedure, in our opinion, is justified only in the presence of a malignant growth.

Of the various procedures directed at the cardia, probably the most rational is esophagogastrostomy. This was first performed successfully

<sup>78</sup> Radlinski. *Observations de chirurgie œsophagienne*, Bruxelles-med 17 202 1936.

in a case of achalasia by Heyrovsky,<sup>10b</sup> in 1912 Gosset,<sup>79</sup> in 1903, had suggested this procedure for strictures of the cardia and had demonstrated its feasibility in cadavers and dogs, using a transpleural approach. The operation as performed by Heyrovsky consists of exposure of the stomach through a laparotomy incision and mobilization of the cardia and esophagus for a distance of about 8 cm, followed by a side to side anastomosis between the esophagus and the stomach, short-circuiting the cardiac orifice. Because, as was emphasized by Frey,<sup>80</sup> in this type of procedure a spur remains at the cardia which may cause some obstruction to the free passage of ingested material from the esophagus into the stomach, Grondahl,<sup>81</sup> in 1916, modified the operation so that the anastomosis is made similar to that of the Finney gastroduodenostomy. In this way the cardiac spur is destroyed and a much wider opening

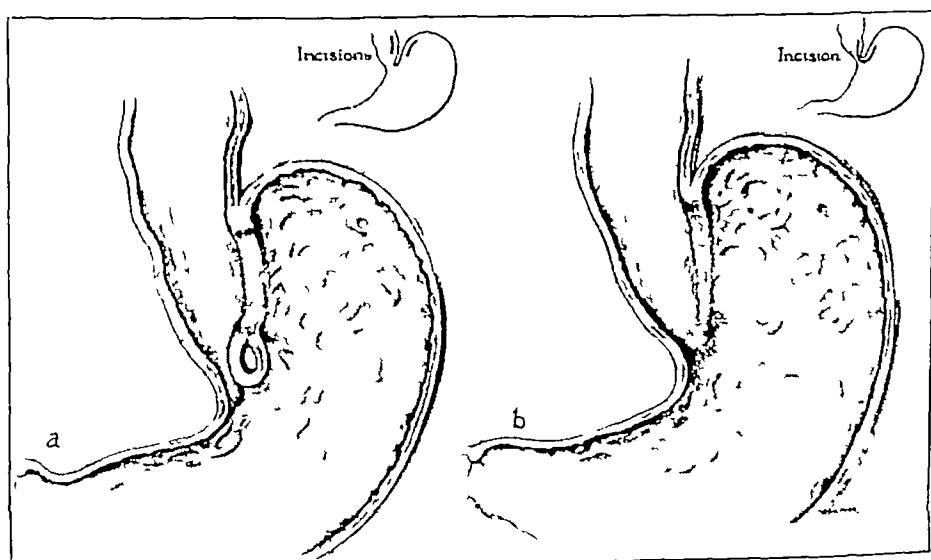


Fig 7—Differences in (a) the original Heyrovsky side to side esophago-gastrostomy and (b) Grondahl's modification. Whereas in *a* a spur remains at the cardia which may cause some obstruction to the free passage of ingested material from the esophagus into the stomach, in *b* the cardiac spur is destroyed and a much wider opening is created between the esophagus and stomach.

79 Gosset, A. De l'oesophago-gastrostomie transdiaphragmatique operation de Biondi, *Rev de chir* 28 694, 1903.

80 (a) Frey, E. K. Zur Technik der Oesophagogastronomie, *Zentralbl f Chir* 59 845, 1932, (b) Zur Behandlung des Kardiospasmus, *Arch f klin Chir* 186 466, 1936. (c) Frey, E. K., and Duschl, L. Der Kardiospasmus, *München med Wchnschr* 84 1374, 1937. (d) Frey, E. K. Die cardioplastische Oesophago-Gastrostomie, *Zentralbl f Chir* 65 2, 1938.

81 Gröndahl, N. B. Plastic Operation for Cardiospasm, *Nord kir förhandl* 11 236, 1916.

is created between the esophagus and the stomach (fig 7) In the United States, Lambert,<sup>82</sup> in 1913, achieved the same end by crushing the spur with a forceps After the cardia and the esophagus were exposed, a large crushing forceps was introduced into the stomach through a gastrostomy opening and applied in such a way that one blade was inserted through the cardia into the esophagus and the other into the fundus of the stomach The clamp was closed, and a few interrupted sutures were used to approximate the esophagus and the stomach about it On the eighth postoperative day the spur had been crushed, and the clamp was removed Instead of a crushing clamp, Keller<sup>83</sup> used a heavy fish line to cut through the spur

Because this procedure of esophagogastrostomy is considered the most rational, a fuller description of the operation is deemed justifiable Whereas some surgeons<sup>84</sup> prefer the transpleural supradiaphragmatic approach, others<sup>85</sup> consider the abdominal approach better In our opinion the abdominal approach is more desirable, because the peritoneum is more resistant to infection than is the pleura, and the exposure is just as satisfactory As has been emphasized by Lambert<sup>82</sup> and others,<sup>86</sup> division of the left lateral hepatic ligament should be made in order to permit retraction of the left lobe of the liver and better exposure of the cardia (fig 8a) The peritoneum over the esophagus is circumcised at the site of its reflection on the diaphragm, and by sharp and blunt dissection the esophagus is freed circumferentially (fig 8b) A

<sup>82</sup> Lambert, A V S (a) Oesophago-Gastrostomy for Cardiospasm, *Ann Surg* 58 415, 1913, (b) Treatment of Diffuse Dilatation of the Oesophagus by Operation Description of a Hitherto Unpublished Method, Report of a Case, *Surg Gynec. & Obst* 18 1, 1914

<sup>83</sup> Keller, W L Operative Relief of Cardiospasm Where Dilatation Has Failed, *Ann. Surg* 88 58, 1928

<sup>84</sup> (a) Sauerbruch, F, in discussion on Kümmell,<sup>50d</sup> *Verhandl. d. deutsch. Gesellsch. f. Chir* 45 149, 1921, (b) Der Kardiospasmus, in *Chirurgie der Brustorgane*, Berlin, Julius Springer, 1925, vol 2, p 572 (c) Sauerbruch, F, and O'Shaughnessy, L Thoracic Surgery, Baltimore, William Wood & Company, 1937 (d) Breitner, B Oesophagogastronomie wegen Kardiospasmus, *Wien med. Wchnschr* 78 765, 1928, (e) Ein durch Esophagogastronomie geheilter Fall von Kardiospasmus, *ibid* 79 508, 1929, (f) Bericht über einen weiteren Fall von Oesophago-Gastrostomie, *ibid* 80 90, 1930 (g) Denk, W, in discussion on Schnitzler<sup>81c</sup> (h) Enderlen Demonstration eines Präparates von Magenoesophagus-anastomose, *Zentralbl. f. Chir* 40 92, 1913 Frey<sup>80</sup>

<sup>85</sup> Oberthur<sup>87a'</sup> Turner<sup>87c'</sup> Turner<sup>87d'</sup> Lambert<sup>82a</sup>

<sup>86</sup> (a) Prat, D Deux cas de megaoesophage, *Bull. et mem. Soc. nat. de chir.* 50 319, 1924 (b) Herzberg, B Die Anatomie des Bauchabschnittes der Speiseröhre, *Deutsche Ztschr. f. Chir* 242 265, 1934, (c) Vergleichende Darstellung verschiedener Methoden operativer Freilegung des Bauchabschnittes der Speiseröhre im Lichte anatomischer und klinischer Untersuchungen, *ibid* 242 290

<sup>87</sup> Footnotes 67 s, v, j, z, a', c' and d'

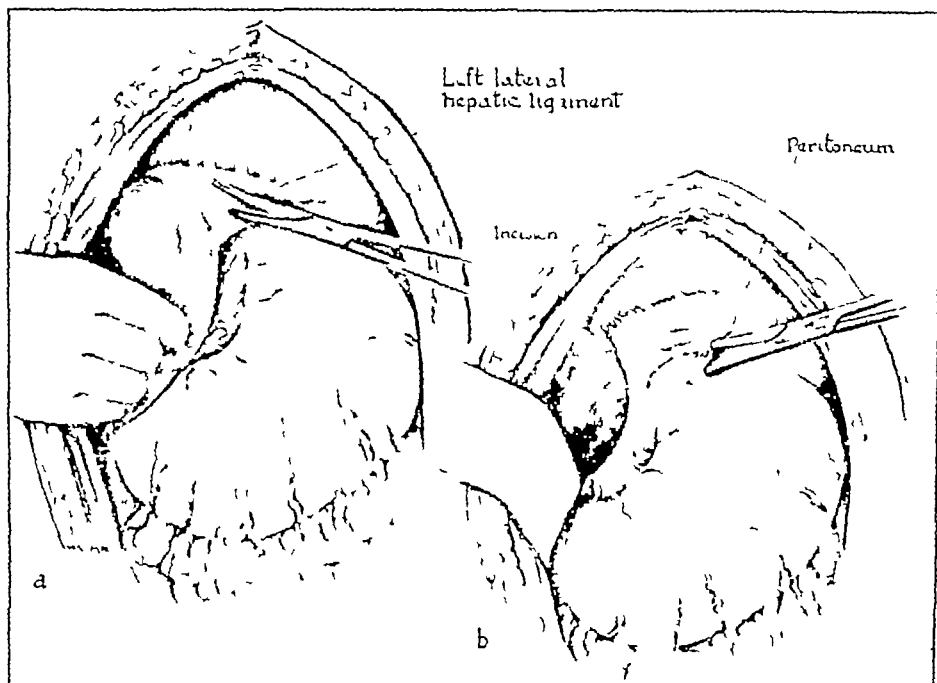


Fig 8—Technic of esophagogastrostomy in the treatment of achalasia Through an abdominal incision the left lateral hepatic ligament is divided in order to permit retraction of the left lobe of the liver and better exposure of the cardia (a) The peritoneum over the esophagus is circumcised at the site of its reflection on the diaphragm, and by sharp and blunt dissection the esophagus is freed circumferentially (b)

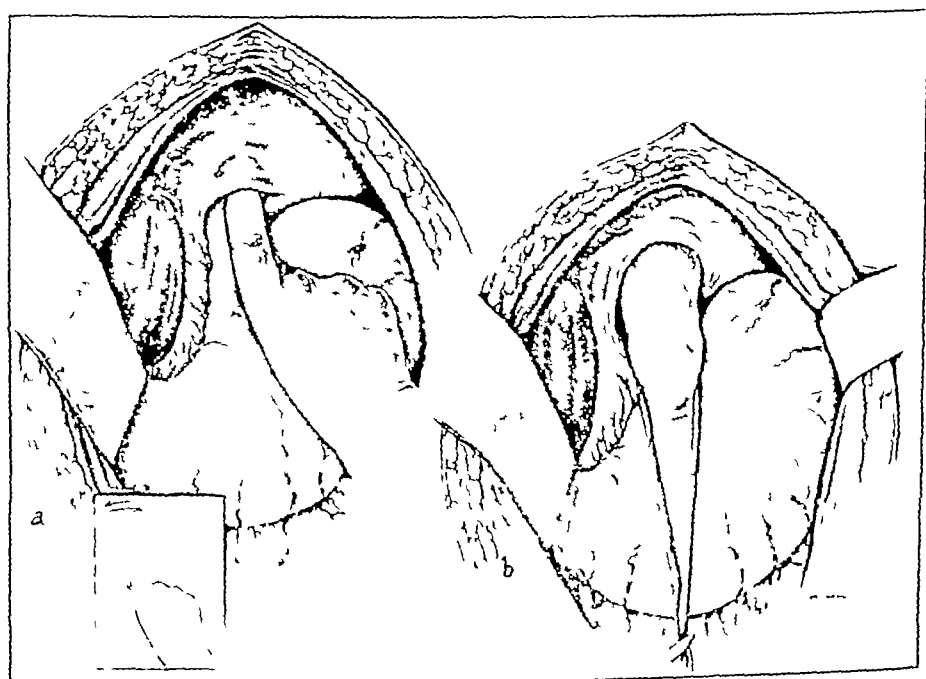


Fig 9—Continuation of the procedure shown in figure 8 The esophagus is carefully mobilized (a) by blunt dissection with the index finger, with the motions shown in the inset Traction on a sling of umbilical tape placed around the esophagus aids in its mobilization (b) as it is gradually pulled down into the peritoneal cavity for approximately 8 to 10 cm

sling of umbilical tape is then placed around it to permit traction downward on the esophagus. By blunt dissection with the index finger the esophagus is mobilized from its hiatus and gradually pulled down into the peritoneal cavity for a distance of approximately 8 to 10 cm (fig 9). At the uppermost portion of the mobilized esophagus a strip of umbilical tape is tied tightly around the esophagus, a technical suggestion made

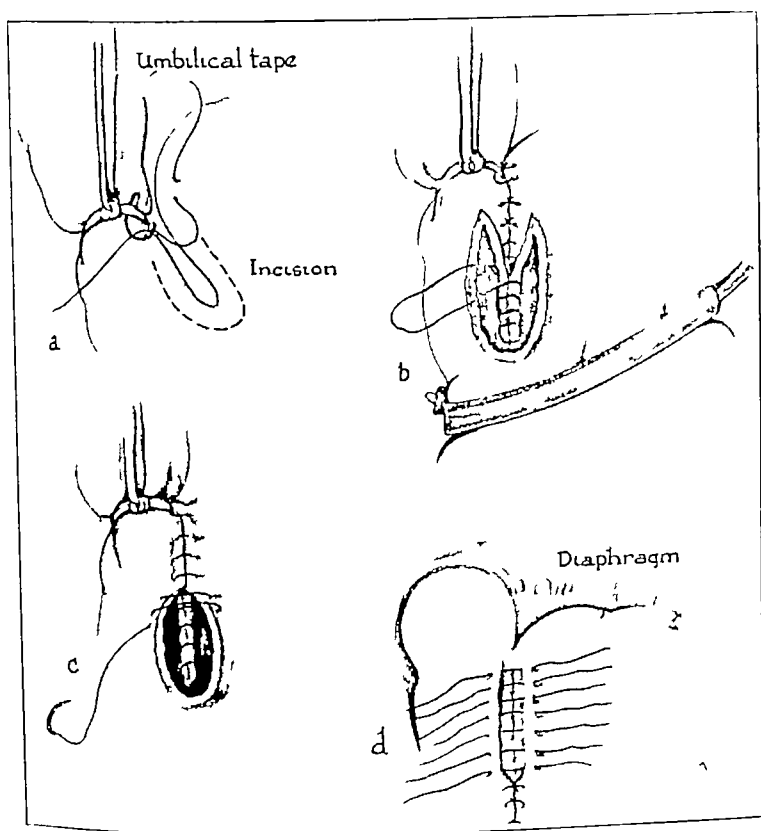


Fig 10—Continuation of the procedure described in figure 9. A strip of umbilical tape is tied tightly (a) around the uppermost portion of the mobilized esophagus. This serves the purpose of preventing spillage from the esophagus and is used to anchor the fundus of the stomach to the esophagus by placing the anchor suture around the tape and thus to obviate tearing the friable esophageal wall. The dotted line shows the site of the incision through the stomach and the esophagus. A rubber-covered clamp is applied (b) to the stomach below the site of anastomosis to prevent spillage. After placing of the first posterior row of interrupted cotton sutures the stomach and esophageal walls are incised as indicated and the second posterior row of sutures is applied with a through and through stitch with no 00 chromic catgut on an atraumatic needle. Then (c) this is brought anteriorly as a Connell stitch. A final row of interrupted Lambert cotton sutures is applied (d), and a few interrupted sutures are used to tack the diaphragm to the fundus of the stomach.

by Fromme<sup>87</sup> (fig 10 *a*) This serves two purposes It prevents spillage from the esophagus above, and it is used to anchor the fundus of the stomach to the esophagus by placing the anchor suture around the tape, thus obviating tearing the friable esophageal wall at a point where there is considerable tension A posterior row of interrupted quilting cotton sutures<sup>88</sup> is installed (fig 10 *b*) Paralleling this row of sutures, an incision is made through the stomach and the esophagus and carried through the cardia The second posterior row of sutures is applied as a through and through stitch with 00 chromic catgut on an atraumatic needle (fig 10 *b*) This is brought anteriorly as a Connell stitch (fig 10 *c*) A final row of interrupted Lambert cotton sutures is applied, thus completing the anastomosis (fig 10 *d*) A few interrupted cotton sutures are used to tack the diaphragm to the esophagus and to the fundus of the stomach in order to avoid traction on the suture line The piece of tape tied around the esophagus is cut and removed An omental graft may be used over the anastomosis as suggested by Palugyay<sup>89</sup> Preliminary paralysis of the right leaf of the diaphragm by phrenicoexeresis or phrenicopraxis has been advocated by some<sup>90</sup>

We have collected from the literature 88 cases in which esophago-gastrostomy has been done for achalasia<sup>91</sup> There were 5 deaths (66

87 Fromme, A Ueber Ursachen und Behandlungsmethoden des sogenannten Kardiospasmus auf Grund klinischer Erfahrung, Beitr z klin Chir **162** 337, 1935

88 Meade, W, and Ochsner, A Spool Cotton as a Suture Material, J A M A **113** 2230 (Dec 16) 1939, The Relative Value of Catgut, Silk, Linen and Cotton as Suture Materials, Surgery **7** 485, 1940

89 Palugyay, J Die Oesophago-Gastro-Anastomose nach Heyrovsky im Röntgenbild Ein Beitrag zum funktionellen Verhalten der Speiseröhre und des Magens nach der Operation, Arch f klin Chir **125** 554, 1923

90 Jirasek<sup>571'</sup> Turner<sup>67c'</sup> Frey<sup>80</sup> Footnotes 84 *d*, *e* and *f*

91 (a) Demmer, F Kardiospasmus, Wien klin Wchnschr **25** 1928, 1912 (b) Exner, A Beitrag zur subphrenischen Oesophago-gastrostomie, *ibid.* **30** 886, 1917 (c) Schnitzler, J Subphrenische Oesophagogastrastomie, *ibid.* **31** 768, 1918 (d) Finsterer, H, in discussion on Kummel,<sup>50d</sup> Verhandl d deutsch Gesellsch f Chir **45** 148, 1921, (e) Zur Therapie des Kardiospasmus und der Kardiastenose, Wien klin Wchnschr **35** 471, 1922 (f) Zaaier, J H, cited by Häggstrom<sup>91m</sup> (g) Nystrom, cited by Häggstrom<sup>91m</sup> (h) Gerulanos, cited by Haglund. (i) Michaelsson, cited by Haggstrom<sup>91m</sup> (j) Toole, H Ein Fall von hochgradigen Kardiospasmus geheilt durch Oesophagogastrastomie, Arch f klin Chir **151** 761, 1928 (k) Giertz, K. H Dilatio esophagi idiopathica Svensk kir sekt forh, 1929, cited by Häggstrom,<sup>91m</sup> (l) Operation of Case of Idiopathic Dilatation of the Esophagus **93** 190, 1931 (m) Häggstrom, P Zwei Fälle von Kardiospasmus und Osophagus-Dilatation, die mit glucklichen Ausgang nach Heyrovsky operiert wurden, Acta chir Scandinav **66** 345, 1930 (n) Correa Netto, A Do tratamento do cardiospasmio pela gastro-esophago-anastomose infradiaphragmatic (operação

per cent) and only 1 poor result. In addition, we have successfully employed this procedure in 2 cases. An interesting feature in the results of this operation (as well as some of the others) is the observation made by numerous surgeons that functionally the patients are considerably better than the roentgen studies would indicate. Thus, in many cases the esophagus appears still dilated after operation, although the patient is able to swallow normally.

Because one of the theories of achalasia incriminates the diaphragm, it was logical to assume that the condition might be corrected by an operative procedure directed at this structure. In 1914, Bassler<sup>30a</sup> proposed division of the diaphragmatic crura on the assumption that spasm of the muscle fibers was the cause of the obstruction. This was done by Braine and Metivet,<sup>92</sup> with a good immediate result. In France this procedure seemed popular. In 1933, Vampre stated that after performing this operation in 5 or 6 cases with poor results he was forced to the conclusion that it is based on a false premise. In addition to enlarging the diaphragmatic hiatus, a number of surgeons have emphasized the importance of drawing the esophagus down and "straightening it out." Apparently this was first suggested by von Hacker<sup>93</sup> in 1913. Whereas some<sup>94</sup> have stressed the importance of this, apparently they are not fully convinced of its value, as they also perform a cardioplasty. Turner<sup>6,c'</sup> stated that he finally discontinued using this procedure after obtaining only 1 good result in 5 cases. Phrenicoexeresis<sup>57b'</sup> has also been done, but the results were unsatisfactory. In the 21 collected

- de Heyrovsky), *Bol Soc de med e cir de São Paulo* **15** 229, 1931 (o) von Haberer, H. Beitrag zur kardiotonischen Speiseröhrenerweiterung, *Zentralbl f Chir* **58** 2947, 1931 (p) Urrutia, L. Cuestiones gastroenterologicas, San Sebastian, Spain, Nueva Editorial, 1931 (q) Fromme, A. Ueber weitere Erfahrungen bei der Behandlung des Kardiospasmus, *Zentralbl f Chir* **60** 3632, 1933 (r) Hansen, J. Beitrag zum Kardiospasmus des Kindesalters, *Beitr z klin Chir* **157** 617, 1933 (s) Churchill, E. D. Oesophageal Surgery, *Surg, Gynec & Obst* **60** 417, 1935 (t) Haglund, A. L. Esophago-Gastrostomies According to Method of Heyrovsky, *Acta chir Scandinav* **76** 109, 1935 (u) Ferrari, R. C., and Itoiz, O. A. La esofagogastrostomia u operación de Heyrovsky, *Bol y trab, Soc de cir de Buenos Aires* **20** 773, 1936 (v) Brea, C. A. Megaesófago por cardiospasma. Su tratamiento por la esofagogastrostomia, *ibid* **21** 733, 1937 (w) Calcagno, B. N., and Belleville, G. Megaesofago. Esofagogastrostomia, *ibid* **21** 747, 1937 (x) Womack, N. A. Esophagoplasty for Esophageal Achalasia, *S Clin. North America* **18** 1241, 1938 (y) Notti, P., and Miyara, S. Operacion de Heyrovsky. Su aplicacion y resultado in un caso de estenosis del esofago abdominal (cardiospasma), *Bol y trab, Soc de cir de Buenos Aires* **23** 298, 1939 (z) Harris R. I., cited by Janes<sup>81</sup> (a') Wilson, G., cited by Janes<sup>81</sup> *Bull* <sup>1b</sup> Janes<sup>81</sup> Heyrovsky<sup>16b</sup> Footnotes 57 o, w and 1' Footnotes 67 m, c', d', u', v', w' and 1" Frey<sup>60</sup> Grondahl<sup>81</sup> Lambert.<sup>82</sup> Keller<sup>83</sup> Footnote 84 Fromme.<sup>87</sup>
- 92 Braine and Metivet, cited by Gregoire<sup>1d</sup>
- 93 von Hacker, cited by von Hacker and Lotheissen<sup>1d</sup>
- 94 Footnotes 67c' and f' Sencert and Simon<sup>71c</sup>

cases<sup>95</sup> in which phrenotomy and transposition of the esophagus were done there were no deaths, and the results were stated as good in 12 (57.1 per cent), as showing improvement in 3 (14.3 per cent), and as failures in 6 (28.5 per cent). It is significant that in 2 of the cases in which improvement took place the authors regretted that they had not performed a plastic procedure<sup>96</sup>. Also of interest is the fact that among the cases in which the results were good there was only 1 with a follow-up longer than a few months.

As has been stated, a number of clinical and experimental observations have been presented in an attempt to explain the pathogenesis of achalasia on the basis of a nervous mechanism. It was therefore assumed that the condition might be corrected by surgical procedures directed at the nerve supply of the esophagus. In general, such procedures may be classified into those attacking the vagus nerves and those attacking the sympathetic nervous system. In 1911, Meyer<sup>97</sup> performed esophageal plication but in addition emphasized the importance of division of the vagal fibers entering the esophagus. However, the results in his cases were poor, and he finally concluded that the best treatment is cardioplasty. Sauerbruch<sup>84a,b</sup> also performed bilateral vagotomy through a transpleural approach in 4 cases. One of the patients died of pleuritis, 1 had a recurrence after a year, and the other 2 had recurrences after a very short period. On the basis of his experience Sauerbruch concluded that vagotomy is not justified and that its rationale is based on a false conception. Rieder's<sup>98</sup> patient became worse after the operation. Pieri,<sup>99</sup> in 1932, through a posterior mediastinotomy iso-

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95 (a) Lardenvois, G, and Braine, J. Phrenospasme chronique lie a un ulcus gastrique juxta-cardiaque. Dysphagie chronique grave avec dilatation de l'oesophage. Echece de dilatations repetees. Gastrostomie. Persistance des troubles. Decouverte operatoire par voie thoracique de la traversee phrenique de l'oesophage. Debridement de l'orifice diaphragmatique. Guerison de la dysphagie, Bull et mem Soc nat. de chir **49** 937, 1923. (b) Kummer, E. Stenose du segment diaphragmatique de l'oesophage. Phrenotomie par le procede de M. Raymond Gregoire (thoracolaparotomie extrasereuse). Guerison, *ibid* **53** 231, 1927. (c) Lefevre and Joncheres. Cardiospasme de l'oesophage traite par la voie thoracoabdominale extra-sereuse de Gregoire, Bull et mem Soc de med et de chir de Bordeaux (1926), 1927, pp 263-267. (d) Hartmann, in discussion on Delbet<sup>97a</sup>. (e) Chenut, M. A. Un case de megaoesophage traite par l'operation de R. Gregoire, Bordeaux chir **3** 510, 1932. (f) Rochet, P. A propos de l'operation de Heller pour cardiospasme, Lyon chir **36** 389, 1939. Scrimger<sup>98</sup> Enderlen<sup>97b</sup>. Footnotes 67 *l, s, l* and *r'*. Braine<sup>75d</sup> Prat<sup>86a</sup> Braine and Metivet<sup>92</sup>.

96 Prat<sup>86a</sup> Lefevre and Joncheres<sup>95c</sup>.

97 Footnotes 40 and 41.

98 Rieder, W, discussion on Fromme,<sup>97w</sup> Arch f klin Chir **157** 137, 1929, Klinik und Therapie des sogenannten Cardiospasmus, Deutsche Ztschr f Chir **222** 47, 1930, footnote 23 c.

99 Pieri, G. Sulla cura del cardiospasmo, Cong Soc internat de chir, Rap **1** 778, 1932, Contributi clinici alla chirurgia del sistema nervoso vegetativo, la cura della acalasia esofagea (cardiospasmo), Arch ital di chir **35** 644, 1933.



lated both vagus nerves and sectioned the fibers entering the lower part of the esophagus. One of the patients, who also had a carcinoma, died of starvation and cachexia several months after operation. A satisfactory result was obtained in a second case, although the patient had empyema. That Pieri was not entirely convinced of the value of this procedure is evinced by the fact that he performed the Heller procedure in 2 subsequent cases. Jirasek<sup>71</sup> reported a case in which the immediate result following bilateral vagotomy was good but in which recurrence subsequently took place. In the 11 collected cases in which vagotomy was done, 3 patients died, there were 7 recurrences, and a satisfactory result was noted in only 1 instance.

On the assumption that the obstruction is due to a functional disturbance of Auerbach's plexus, which innervates the circular musculature of the cardia, Recalde,<sup>100</sup> in 1924, advocated decortication of the plexus. In this way he attempted to interrupt the sympathetic nerve supply of the cardia. Of the 4 patients on whom he performed this operation, 1 died of peritonitis following accidental perforation of the esophageal musculature, and the other 3 had good results. One of these had been operated on sixteen years previously by the Heller technic and had had a recurrence. A number of observers had indicated that the sympathetic nervous system may play a significant role in the pathogenesis of this condition. However, it was not until 1934 that this contention was placed on a firmer support by the results of Knight's<sup>101</sup> experimental investigations. He showed that in cats there exists a true sphincter mechanism at the cardia, that bilateral vagal section reproduces the appearance of achalasia, which can be prevented by simultaneous removal of the sympathetic fibers, and that the condition can be relieved by sympathectomy after it has been produced experimentally. On this basis sympathectomy was performed in 5 cases of achalasia reported by Knight<sup>102</sup> and Adamson.<sup>103</sup> Because in dissections of cadavers it was found that the sympathetic nerve supply to the cardiac sphincter is derived chiefly from the left side of the celiac plexus and distributed along the left gastric artery, Knight advocated excision

100 Recalde, J. F. (a) Sobre um caso de mal de engasgo curado cirurgicamente, *Bol. Soc. de med. e cir. de São Paulo* 7:78, 1924, (b) Cardiospasmio, disfagia e megaesofago, simpaticectomia esofagica (statistica chirurgica) *Arch. ital. di chir.* 32:613, 1932.

101 Knight, G. C. The Innervation of the Esophagus. *Proc. Roy. Soc. Med.* 28:891, 1935, footnote 22 c.

102 Knight, G. C. Sympathectomy in the Treatment of Achalasia of the Cardia. *Brit. J. Surg.* 22:864, 1935, Sympathectomy for Achalasia of the Cardia. *Proc. Roy. Soc. Med.* 28:897, 1935.

103 Adamson, W. A. D. Sympathectomy for Achalasia of the Cardia. *Proc. Roy. Soc. Med.* 28:892, 1935.

of this artery, with its surrounding fat and nerve tissue. Of the 5 patients reported on by Knight and Adamson and treated in this manner, 1 was completely relieved, 1 was considerably improved and the other 3 showed signs of recurrence. Whereas the majority of surgeons have employed the procedure of Knight in the attack on the sympathetic nervous system, Craig, Moersch and Vinson<sup>104</sup> used a different technic. They performed sympathectomy by bilateral resection of the cervicothoracic sympathetic ganglions and trunk, with a good immediate result. Prior to the operation a diagnostic procaine hydrochloride block of the cervicothoracic sympathetic ganglions was done, and the patient was temporarily relieved, which indicated that the operation would be successful. In the 19 collected cases<sup>105</sup> of achalasia, including ours, in which sympathectomy was done there were 1 death<sup>100b</sup> due to peritonitis following accidental rupture of the mucosa and 1 due to suicide<sup>571</sup>. Recurrence took place in 4 cases, and improvement was only partial in 4. The results in these cases were not impressive. Mitchell<sup>106</sup> expressed the opinion that the high incidence of failures following these procedures may be explained on the basis of the great anatomic variation in the sympathetic nerve supply to the cardia and the consequent difficulty of interrupting the sympathetic pathways. In 1 of our cases a diagnostic procaine hydrochloride block by the anterior approach<sup>107</sup> was followed by rapid passage of barium sulfate through the cardia as determined fluoroscopically. Subsequently a bilateral cervicodorsal sympathectomy was performed, and, although the patient showed immediate improvement following the operation, several weeks later there was complete recurrence of the condition. The patient is to return for esophagogastronomy.

Because of its anatomic location, adequate exposure of the cardia meets with relative technical difficulty. For this reason a number of surgical approaches have been devised. In general, these may be clas-

104 Craig, W., Moersch, H. J., and Vinson, P. P. Treatment of Intractable Cardiospasm by Bilateral Cervicothoracic Sympathetic Ganglionectomy. Report of a Case, *Proc. Staff Meet., Mayo Clin.* 9:749, 1934.

105 Rupp, in discussion on Frey,<sup>80b</sup> *Arch. f. klin. Chir.* 186:19, 1936. Souttar, H. S. Oesophageal Obstruction, *Brit. M. J.* 2:777, 1935. Eliason, E. L., and Erb, W. H. Cardiospasm. Report of Two Cases Treated by Resection of Sympathetic Supply to the Cardiac Sphincter, *Am. J. Surg.* 35:105, 1937. Stubbe, H. Oesophageal Achalasia Treated by Sympathectomy, *M. J. Australia* 2:1001, 1937. Meade, H. S. A Case of Sympathectomy in the Treatment of Achalasia of the Cardia, *Irish J. M. Sc.*, 1939, p. 130. Gray and Skinner<sup>571</sup>. Recalde<sup>100</sup>. Knight<sup>101</sup>. Knight<sup>102</sup>. Adamson<sup>103</sup>. Craig and others<sup>104</sup>.

106 Mitchell, G. A. G. The Nerve Supply of the Gastro-Oesophageal Junction, *Brit. J. Surg.* 26:333, 1938.

107 Ochsner, A., and DeBailey, M. Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, *Surgery* 5:491, 1939.

sified into transabdominal and transthoracic<sup>108</sup> Of the former there are two types those in which exposure is obtained through a high median or a left paramedian incision and those in which the left costal arch is mobilized The majority of surgeons have used the former, and in our opinion this is usually sufficient In some cases this is combined with partial mobilization of the costal cartilage near the sternum and division of this cartilage at this site<sup>109</sup> Others have preferred a subcostal incision parallel to the costal margin, similar to that described by Fenger in 1854 Still others have contended that a more satisfactory exposure of the cardia may be obtained by mobilization of the costal arch In 1887, Lannelongue<sup>110</sup> proposed mobilization of the costal arch by resection of segments of the lower four or five ribs and their cartilages anteriorly Working on cadavers, Micheli,<sup>111</sup> in 1895, modified this procedure by using a Schede type of incision and simply dividing the ribs medially and laterally so that the resultant flap could be thrown up In 1898, von Mikulicz<sup>112</sup> employed a somewhat similar approach in a case of carcinoma of the cardia, and in another case he used multiple transverse incisions over the respective costal cartilages in order to expose and divide them Somewhat similar approaches were used more recently by Lambert<sup>82</sup> and by Churchill<sup>91a</sup> Such procedures are so extensive that the approach alone is sufficient to put the patient in shock In fact, Wiener,<sup>113</sup> in 1908, suggested dividing the operation into stages, with mobilization of the costal arch as the first stage Kelling also desired to avoid the shock associated with these procedures but proposed a method which was apparently worse In 1901 he<sup>114</sup> recommended increasing the subdiaphragmatic exposure by the patient's posture, recommending one in which the lower part of the abdomen and the extremities hung vertically over the end of the table Apparently

108 Ochsner, A, and DeBakey, M Carcinoma of the Esophagus, J Thoracic Surg, to be published

109 Ferrari, R C La esófago-gastrostomía por vía abdominal u operación de Heyrovsky Técnica operatoria, Semana med 1 1539, 1936, La cardiostomía extramucosa (operación) Técnica operatoria, ibid. 1 1081, 1936 Clute, H M, and Albright, H L Cutting the Costal Arch for Upper Abdominal Exposure, Surg Gynec & Obst. 67 804, 1938 Footnotes 91 *u*, *v* and *w*

110 Lannelongue Les abcès tuberculeux perihepatiques et leur traitement Semaine med. 7 235, 1887

111 Micheli, cited by Wiener<sup>113</sup>

112 von Mikulicz, J Beiträge zur Technik der Operation des Magencarcinoms, Verhandl d deutsch Gesellsch f Chir 2 252, 1898, Beiträge zur Technik der Operation des Magencarcinoms, Arch f klin Chir 57 524, 1898

113 Wiener, J Osteoplastic Resection of the Costal Arch Followed by Resection of Lesser Curvature of Stomach and Esophagus and Esophagostomy Ann Surg 48 530, 1908

114 Kelling, G Becken-Hängelage bei horizontalem Rumpf für Operationen in der Nähe des Zwerchfells, Zentralbl f Chir 28 1025, 1901

even he found this unsatisfactory, because several years later he suggested another posture<sup>115</sup> Although Marwedel's<sup>70</sup> and Asthoewer's<sup>116</sup> publications appeared in the same year, 1903, the former preceding the latter by a few months, Asthoewer apparently deserves priority He stated that in 1894 he operated on a patient with fibroma of the spleen He first made a left rectus incision, but because of the size of the tumor it was necessary to obtain greater exposure He accomplished this by converting the incision into the shape of a U and then dividing the ribs from the eighth to the tenth laterally and their fused cartilages medially The resultant osteoplastic flap could be mobilized upward In a second case, in which there was a sarcoma of the left side of the thoracic wall, he used a paracostal incision and divided the seventh costal cartilage near its attachment to the sternum and the eighth through the tenth ribs in the midaxillary line Marwedel used a paracostal incision and through this exposed and divided the seventh cartilage near the sternum and the seventh, eighth and ninth ribs near the chondrocostal junction In 1906, Meyer<sup>117</sup> employed a similar approach but made a right-angled incision Undoubtedly mobilization of the costal arch increases the exposure, but because of the increased extent and duration of operation its use is seldom justified Moreover, because of mobilization of the chest wall there is greater likelihood of postoperative morbidity

*Transpleural Approach*—Although Biondi,<sup>118</sup> in 1895, suggested the transpleural approach for resection of the cardia for malignant disease of this portion of the esophagus, Gosset,<sup>79</sup> in 1903, advocated the transpleural approach for resection of the cardia for nonmalignant disease of this area He performed this operation on cadavers and on animals The operation which he proposed and performed experimentally consisted of a side to side anastomosis between the dilated esophagus and the fundus of the stomach Meyer,<sup>97</sup> in 1911, performed vagolysis of the esophagus transpleurally Because of a recurrence the following year, he performed a transpleural cardioplasty Henschen,<sup>119</sup> working in Sauerbruch's clinic, performed the first successful esophago-gastrostomy by the transpleural route This case was subsequently

115 Kelling, G Technische Beiträge zur Chirurgie der Bauchhöhle, Zentralbl f Chir **31** 90, 1904

116 Asthoewer Die Aufklappung des Rippenbogens zur Erleichterung operativer Eingriffe im Hypochondrium und Zwerchfellkuppelraum, Zentralbl f Chir **30** 1257, 1903

117 Meyer, W Osteoplastic Resection of the Costal Arch in Order to Reach the Vault of the Diaphragm, J A M A **47** 1069 (Oct 6) 1906 Meyer, H W Osteoplastic Resection of the Costal Arch for Gunshot Wound of Spleen, Surg, Gynec & Obst **48** 412, 1929

118 Biondi, D Esofago-gastrostomia sperimentale intrathoracica, Policlinico (supp) **1** 964, 1895

119 Henschen, in discussion on Frey,<sup>80b</sup> Arch f klin Chir **186** 20, 1936

referred to in Sauerbruch's publication Denk,<sup>84b</sup> in 1918, reported an esophagogastrostomy performed by the transpleural route. Sauerbruch popularized the transpleural approach for operations on the cardiac end of the esophagus. The advantages of the transpleural approach are obvious, particularly since it facilitates exposure of the cardiac end of the esophagus and the upper portion of the stomach. This is due to the upward arching of the diaphragm, which makes exposure of this portion of the digestive tract from the abdomen relatively difficult. Another advantage of the transpleural approach is that it is possible to cut or crush the phrenic nerve at the time of the operation without any difficulty. On the other hand, transpleural exposure of the lower end of the esophagus is fraught with many dangers and is more complicated than the usual transabdominal approach. The danger of infection of the pleural cavity, particularly if the esophageal mucosa is open, is much greater than the danger of peritonitis. Of 16 patients<sup>120</sup> operated on by the transpleural approach, 5 died (31.2 per cent). An additional patient had a pleural infection.

A combination of transthoracic and transabdominal approach was suggested in 1933 by Ohsawa,<sup>74</sup> who designated it as a free transdiaphragmatic thoracolaparotomy. The operation was performed through a hook-shaped incision beginning at the junction of the anterior axillary line and the seventh rib, crossing the level of the tenth rib at the posterior axillary line and terminating at the level of the sixth rib at the paravertebral line. The seventh and eighth ribs were resected over a distance of about 7 cm., and the thoracic cavity was entered. After the esophagus had been mobilized, the abdomen was opened by incising the diaphragm from the hiatus outward. This approach undoubtedly gave an excellent exposure, but it appears to us that because of the magnitude of the procedure its use is hardly justified for benign lesions. Gregoire,<sup>121</sup> in 1923, proposed an extraserous approach exposing both the thoracic and the abdominal cavity. There are the same objections to this type of procedure as to the transpleural and the complicated abdominal approaches.

*Anesthesia*—The majority of patients with achalasia who have been operated on have had general anesthesia. Finsterer,<sup>91c</sup> Fromme<sup>6</sup> and Fruchaud<sup>6</sup> advocated splanchnic analgesia combined with either local or light ether anesthesia. South American and Spanish surgeons have preferred spinal analgesia. Although one of our esophagogastrostomies was done with the patient under general anesthesia we are of the opinion that spinal analgesia induced with properly administered nupercaine

<sup>120</sup> Footnotes 67 *to c'* and *d'*. Frey<sup>80</sup> Footnotes 84 *a b d e* and *f*. Prat<sup>82a</sup> Fromme,<sup>67</sup> Meyer<sup>80</sup> von Haberer<sup>91a</sup>

<sup>121</sup> Footnotes 71 *d e, f a, h, i* and *j*

and carefully supervised by a trained anesthetist, as used in our case 2, is the anesthesia of choice. This permits adequate relaxation and analgesia of sufficient duration for the operation to be completed without difficulty.

#### REPORT OF CASES

**CASE 1**—Mrs. A. D., a white woman 44 years of age, was admitted to the Hutchinson Memorial Clinic Sept. 11, 1934, complaining chiefly of difficulty in swallowing, which began suddenly approximately twenty-two years previously. At this time she was three months pregnant. She had difficulty in swallowing both liquids and solids, and the dysphagia was associated with retrosternal pain, dyspnea and smothering sensations. She soon learned that by drinking large quantities of water rapidly immediately after eating and standing erect and straining during expiration she could force some food down. The condition continued with exacerbations until 1932, when a gastrostomy became necessary for feeding purposes. She was treated by bougienage and was temporarily relieved, but the condition soon recurred. She had lost about 20 pounds (9 Kg.) in weight. The past history, family history and social history were not significant. Physical examination revealed her to be thin, poorly nourished and of hyposthenic habitus. She was intelligent and cooperative, with no evidence of nervousness or mental depression. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 120 systolic and 80 diastolic. Detailed physical examination revealed no gross abnormalities except emaciation, retrocele and cystocele.

**Special Tests**—Urinalysis revealed no abnormalities. The Wassermann reaction was negative. There were 4,000,000 red blood cells per cubic millimeter, with 80 per cent hemoglobin, the white blood cell count was 4,000 per cubic millimeter, with 68 per cent neutrophils.

**Roentgen Data**—Fluoroscopic examination of the esophagus after ingestion of barium sulfate (September 14) revealed a marked dilatation of the entire esophagus, with an apparent obstruction at the cardia as only a small amount of barium trickled through into the stomach. The esophagoscope revealed the esophagus markedly dilated and filled with large quantities of foul material. There was no other organic change.

**Progress**—The patient was treated by dilation with mercury bougies. This produced temporary improvement, and she was discharged. However, the condition recurred, and she was readmitted in February 1935. Bougienage therapy again resulted in temporary improvement, and she returned home. She was readmitted a year later with recurrence of the condition and was again treated with mercury bougienage, with results similar to those obtained on previous occasions.

She returned to the hospital in August 1937, stating that her condition was much worse. Roentgen studies on August 7 revealed marked dilatation and tortuosity of the esophagus, with obstruction at the cardia (fig. 11A). On August 18 bilateral procaine hydrochloride block of the stellate ganglions was performed by the anterior approach. Immediately afterward fluoroscopic examination of the esophagus following ingestion of barium sulfate revealed free and rapid passage of the barium mixture through the cardia into the stomach. This indicated that the patient might be relieved by sympathectomy. On August 20, with general anesthesia, the left stellate and the second and third thoracic sympathetic ganglions and the intervening trunk were excised. About ten days later

a similar procedure was performed on the right side. The postoperative course was uneventful, and the patient was able to swallow much better when she was discharged, on October 5. On September 21 roentgen examination following ingestion of a barium sulfate meal had revealed the esophagus as much dilated as before operation, but there was some improvement in the passage of barium through the cardia (fig 11 *B*).

The patient was again observed in February 1938, and at this time her condition was apparently no better than it had been prior to operation. She had

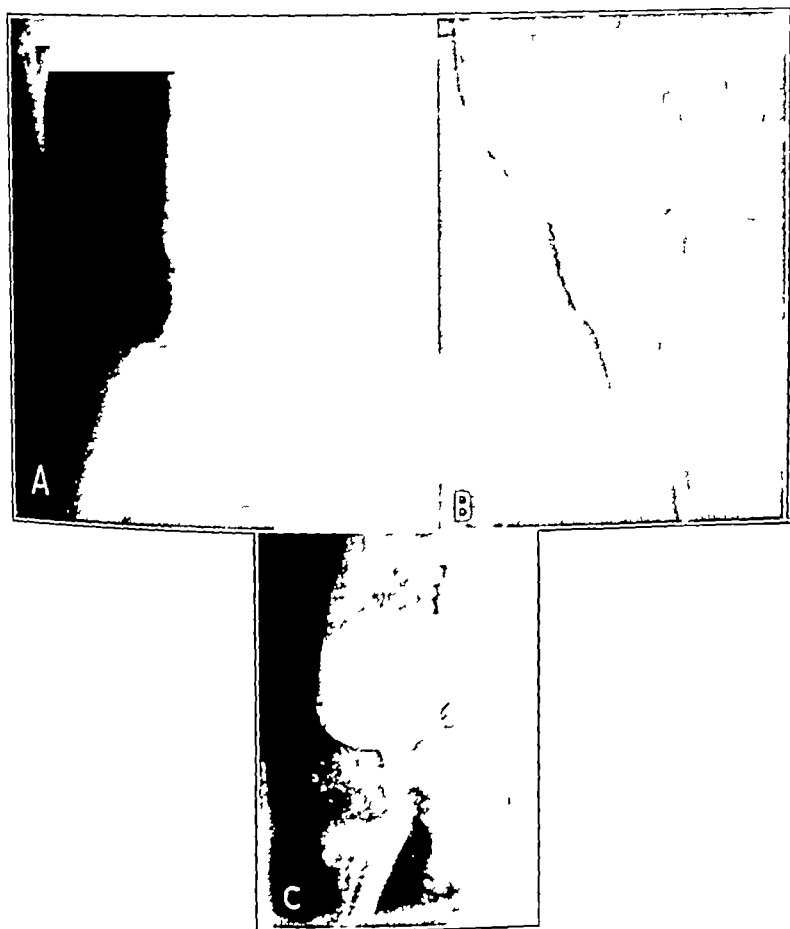


Fig 11 (case 1) —*A*, roentgenogram of the esophagus following ingestion of a barium sulfate meal, showing marked dilatation and tortuosity, with obstruction at the cardia. *B*, roentgenogram of the esophagus and cardia after ingestion of a barium sulfate meal approximately one month after sympathectomy. The dilatation is still present, but there is some improvement in the passage of the barium through the cardia. *C*, roentgenogram of the esophagus and cardia after ingestion of a barium sulfate meal three years after sympathectomy. The dilatation and obstruction remain unchanged.

gained no weight, and there was complete recurrence of the dysphagia. She was again treated by mercury bougienage, with temporary improvement.

She returned to the hospital on July 16, 1940, and roentgen studies revealed the condition to be unchanged (fig 11 C). She is to return for esophagogastrostomy.

**CASE 2**—Mrs E S, a white woman 63 years of age, was admitted to Touro Infirmary on Aug 9, 1939, complaining chiefly of fulness and vomiting after eating small amounts of food. This began thirty-three years previously, and progressively became worse until, at the time of admission, she had difficulty in swallowing fluids. She occasionally had attacks of severe retrosternal pain associated with marked dyspnea. Nine years previously she had been operated on and told that she had an inoperable carcinoma of the stomach. For the past year she had been treated by mercury bougienage with little improvement. She had lost a considerable amount of weight. The past history, social history and family history were not significant.



Fig 12 (case 2)—*A*, roentgenogram of the esophagus after ingestion of a barium sulfate meal, showing enormous dilatation and marked tortuosity of the esophagus, with obstruction at the cardia and practically no leakage of barium into the stomach. *B*, roentgenogram of the esophagus following ingestion of barium sulfate meal after operation. There is a distinct decrease in dilatation, and the barium mixture passes freely and rapidly into the stomach.

Physical examination revealed her to be fairly well developed. She did not appear acutely ill. She was intelligent, cooperative and cheerful. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 120 systolic and 80 diastolic. Detailed physical examination revealed no gross abnormalities.

**Special Tests**—Urinalysis revealed a few pus cells. The Wassermann reaction was negative. The blood picture was normal. The renal function test revealed no abnormality. The electrocardiogram showed slight evidence of myocardial changes. Roentgen studies following ingestion of a barium sulfate meal revealed considerable dilatation and tortuosity of the esophagus. There was definite constriction of and obstruction to the passage of barium at the cardia (fig 12 *A*).



Esophagoscopic study showed the esophagus to be markedly dilated and to contain a large quantity of foul material. There were no other abnormalities, and the cardia could be entered readily.

*Operation*—After adequate preparation, on September 5, with nupercaine spinal analgesia through a left subcostal incision an esophagogastrostomy as described and illustrated in figures 8 to 10 was performed.

*Progress*—The postoperative course was uneventful, and the patient was on a regular diet within ten days after operation. She was discharged on September 22, in excellent condition. She had no difficulty in swallowing any food.

The patient was observed on July 5, 1940, ten months after operation and was found to be in excellent condition. She was able to eat everything with no difficulty and had been completely relieved of all previous manifestations. She had gained 35 pounds (16 Kg). Roentgen studies following ingestion of barium

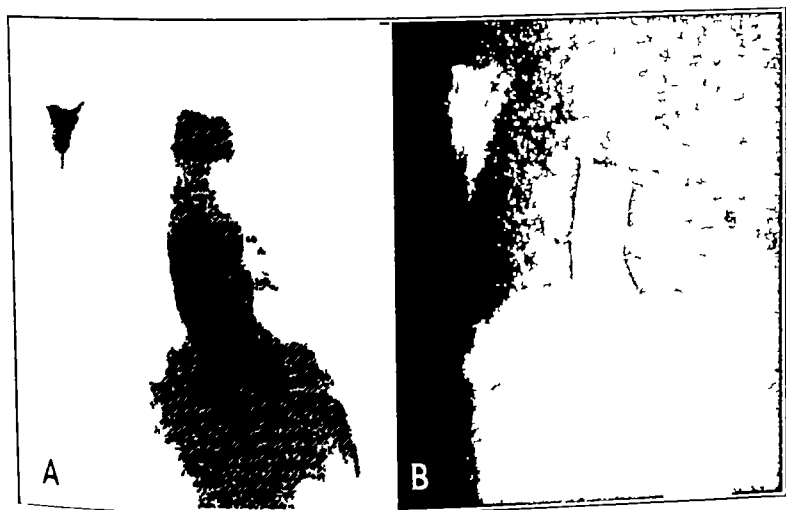


Fig 13 (case 3) —*A*, roentgenogram of the esophagus after ingestion of a barium sulfate meal, showing marked dilatation of the esophagus and constriction at the cardia, with little seepage of barium into the stomach. *B*, roentgenogram of the esophagus after ingestion of barium sulfate after operation. There is definite diminution in the size of the esophagus, and the barium flows readily into the stomach.

sulfate revealed some dilatation, which was less than that observed prior to operation. There was rapid passage of the barium mixture through the cardia (fig 12 *B*).

**CASE 3—B B**, a white boy 9 years of age, was admitted to the Charity Hospital on Nov 29, 1939, complaining chiefly of vomiting food recently ingested. He had begun to have symptoms about one year previously, when it was observed that after eating a part of his meal he had the sensation that it had stopped in the lower part of his chest and that if more were eaten regurgitation would occur. This was not associated with pain or nausea. The condition progressively became worse, with intermittent attacks during which he could swallow only milk. The past history and the family history were not significant.

Physical examination revealed him to be slightly undernourished for his age but quiet, cheerful and cooperative. There were no gross abnormalities. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 105 systolic and 65 diastolic. Detailed physical examination revealed no gross abnormalities.

*Special Tests*—Urinalysis showed no abnormalities. The Wassermann reaction was negative and the blood picture normal. Roentgen studies on July 8 after a barium sulfate meal revealed marked dilatation of the esophagus with obstruction at the cardia and slight seepage of barium into the stomach (fig 13 A). The esophagoscope showed the esophagus markedly dilated and containing large quantities of foul material. There was no other organic change, and passage through the cardia was easily done.

*Progress*—The patient was treated conservatively by mercury bougienage and antispasmodics for several months, with only slight temporary improvement. After this he was discharged but returned to the hospital on May 9 in a worse condition, and it was decided that an operation was necessary. Accordingly, after necessary preparation, on July 11, 1940, with general inhalation anesthesia, through a left subcostal incision an esophagogastrostomy was performed as described and illustrated in figures 8 to 10. The postoperative course was uneventful. One week after operation he was swallowing all liquids normally and within another week he was on a regular diet. He had no complaints and was discharged on July 26. Roentgenologic studies following ingestion of barium sulfate on July 23 had revealed a distinct decrease in the dilatation of the esophagus and free and rapid passage of the barium mixture into the stomach (fig 13 B).

The patient was again observed on August 10 and was found to be in excellent condition, with complete relief of all previous manifestations.

#### SUMMARY

The various factors which have been considered of pathogenic significance in the development of achalasia of the esophagus are briefly reviewed.

The various types of radical procedures which have been advocated and employed are classified into four large groups, depending on whether they are directed at (1) the dilated esophagus, (2) the cardia, (3) the diaphragm or (4) the nerve supply. A brief historical consideration of each procedure is presented. The various operations are described and illustrated, and the collected cases are analyzed.

The procedures directed at the dilated esophagus and based on an attempt to reduce the size of circumference by esophagoplication are irrational and are considered of historical interest only.

Four types of procedures have been directed at the cardia: (1) dilation, (2) plastic operation, (3) excision, and (4) deviation.

Dilation of the cardia has been done by retrograde bougienage and transgastrically by instruments or fingers. In 80 cases collected from the literature in which the latter procedure was used 7 (8.75 per cent) patients died and 8 (10.0 per cent) operations were failures.

The plastic procedures consist of extramucous cardiomyotomy or cardioplasty. In 104 collected cases in which the former was employed there were 4 deaths and 14 recurrences. In 36 cases in which the latter was used there was 1 death and 1 recurrence.

Excision of the cardia followed by esophagogastrostomy has been done in 2 cases, in 1 of which the patient recovered. Such a radical procedure, in our opinion, is justified only in the presence of a malignant tumor.

Of the various procedures directed at the cardia, esophagogastrostomy is considered the most rational. This may be performed either by side to side anastomosis between the esophagus and the fundus of the stomach or, preferably, by an anastomosis, similar to the Finney gastroduodenostomy, which obviates the cardiac spur in the esophagus and thus creates a wider opening between the esophagus and the stomach. In 88 cases collected from the literature in which esophagogastrostomy was performed there were 5 deaths (6.6 per cent) and only 1 poor result.

Operations directed at the diaphragm consist of phrenotomy and mobilization of the esophagus downward. In 21 collected cases in which these measures were used there were no deaths, and the results were stated as good in 12 (57.1 per cent), showing improvement in 3 (14.3 per cent) and failures in 6 (28.5 per cent).

The procedures directed at the nerve supply may be classified into those attacking the vagus nerves and those attacking the sympathetic nervous system. In 11 collected cases in which operations of the former type were done, 3 patients died, 7 recurrences were observed and only 1 satisfactory result was recorded. In 19 collected cases in which operations of the latter type were done there were 1 death due to peritonitis and 1 to suicide. There was recurrence in 4 cases, and partial improvement was observed in 4.

Three cases are reported by us. An esophagogastrostomy was done in 2, with excellent results. A sympathectomy was performed in the other, with recurrence.

# SURGICAL TREATMENT OF CARCINOMA OF THE ESOPHAGUS

JOHN H. GARLOCK, M.D.

NEW YORK

The importance of carcinoma of the esophagus becomes evident when it is realized that in New York city alone it accounts for 3.5 per cent of all deaths from cancer (Watson). In the United States registration area the incidence of cancer of the esophagus increased almost 100 per cent from 1915 to 1932. Clairmont, in 1924, estimated that about 25,000 persons die of this disease annually in Europe. With the realization that cancer of the esophagus is assuming increasing importance from the standpoint of numerical incidence and with the rapid strides being made in the fields of anesthesia and thoracic surgery has come an ever increasing interest in the radical surgical treatment of this disease, based on the present day conception of surgical treatment of cancer in general. It is, however, only in recent years that encouraging progress has been noted. Although at present operative treatment of cancer of the esophagus is being carried out by a relatively small group of surgeons, it is my prediction that within a very few years such treatment will be the accepted method of handling this disease and will be universally adopted.

It must be remembered that, from the pathologic standpoint, carcinoma of the esophagus is usually a slowly growing tumor and that it remains a local disease for some time before metastasizing to the regional lymph nodes. However, although it may not spread peripherally until late, it may become locally inoperable in the early stages because of fixation to a nearby vital structure, such as the aorta or a bronchus. The importance of diagnosis early in the disease needs little discussion. More rapid advance in the surgical treatment of cancer of the esophagus will be made when increasing numbers of early lesions are referred to the surgeon. It is important to stress, therefore, that the physician must regard with suspicion any disturbance in the act of swallowing in a patient past 35 or 40 years of age. Persistent dysphagia calls for careful roentgen examination. In cases of early involvement the roentgenogram may reveal nothing abnormal, especially if the ordinary barium sulfate mixture is used. If a heavier mixture of barium is employed, the mucosal pattern of the esophagus will be more accurately depicted, and an early lesion will be more easily demonstrated. Roentgen examination should include fluoroscopic observations of the activity of the

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From the Surgical Service of the Mount Sinai Hospital

esophagus during the act of swallowing the mixture of barium. Fixation of a portion of the esophageal wall, such as would occur in the presence of a tumor, would be an important diagnostic point. This examination should be supplemented by esophagoscopy. The purpose of this examination is to determine the presence of a neoplasm, to note its gross appearance, to obtain a biopsy specimen of the tumor and to localize the position of the growth with reference to the distance from the upper incisor teeth. The last-mentioned point is of importance because it helps the surgeon to decide which type of operation should be undertaken. No patient should be subjected to radical operation unless positive results have been obtained for biopsy.

Until recent years the diagnosis of cancer of the esophagus was frequently made late in the disease, too late for surgical treatment, and such a diagnosis was synonymous with a fatal prognosis. The accepted method of treatment was by radiation (roentgen and radium), supplemented usually by gastrostomy. An enormous experience with these modalities has accumulated throughout the world, and critical survey of the results is possible. It is fair to state that the results of radiation therapy for cancer of the esophagus have been universally disappointing. Of the vast number of patients treated by these methods, approximately 20 are said to be cured, and the cure of many of these is open to question, either because the follow-up period has been too short or because histologic evidence of the presence of carcinoma has been incomplete or inconclusive. That radiation therapy, whether by local use of radium or by external irradiation, is not without considerable danger is indicated by the numerous reports of perforation of the esophagus with fatal mediastinitis. In a fairly large experience with this disease, I have never seen a case in which radiation therapy has prolonged life beyond the period of the usual life history of the disease, provided that a gastrostomy has been performed for feeding purposes. Ricard and Ballivet crystallized the general opinion among surgeons today when they said that if surgeons had a chance to resect the large number of early lesions now being referred to radiologists, their results would be incomparably better than any the radiologists have been able to report.

Unfortunately, many patients, with cancer of the esophagus are in the sixth and seventh decades of life and associated degenerative diseases of the heart, kidneys and blood vessels may preclude any attempt at radical surgical therapy. It would be foolhardy to subject a patient in his seventies, with a poor heart, arteriosclerosis and poorly functioning kidneys, to the hazards of so extensive a procedure. On the other hand, many patients in these age groups are in excellent condition and can be brought safely through the surgical ordeal. The patient in Forch's famous case is a noteworthy example. Each case should be judged on

its own merits, and the surgeon should have the advice and counsel of a competent physician to aid him in estimating the physical equipment of the patient. The surgical treatment of esophageal cancer is a cooperative problem, involving not only the surgeon but the physician, the esophagoscopist, the anesthetist, the nursing staff and the operating room personnel.

#### PREOPERATIVE PREPARATION

It is most important to prepare the patient thoroughly, so that the risk of the operative procedure may be minimized. Careful attention to oral hygiene will lessen the possibility of pulmonary complications incident to prolonged anesthesia and manipulation of the lobes of the lung. Carious teeth should be extracted and the gums and teeth cleansed. A high caloric liquid diet containing the necessary vitamins and minerals should be given. To combat dehydration, which is frequently present, fluids should be given by venoclysis as well as by mouth. A daily intake of 3,000 cc is desirable. A transfusion of 500 cc of whole blood should be given a day or two prior to operation. As the surface of the carcinoma is ulcerated and covered with highly infectious organisms, every effort should be made to decrease the virulence and number of these bacteria so as to minimize the possibility of mediastinal or pleural infection. I have approached this problem in two ways. As a result of a study of the value of preoperative administration of sulfanilamide in surgical treatment of the colon (with bacteriologic controls), I have routinely administered sulfanilamide to patients with cancer of the esophagus for seventy-two hours prior to operation, in 15 grain (0.97 Gm) doses every four hours. A large experience with these lesions will be the deciding factor in determining the efficacy of this drug as a prophylactic medicament. I cannot agree with the findings of Bricker and Graham that preoperative administration of this drug interferes with wound healing. The only objection to its use that has been encountered, and it is a minor one, is that the cyanosis produced by the drug may upset the anesthetist's estimation of the amount of oxygen required in administration of the anesthesia.

The second line of attack against the bacterial flora of the ulcerated neoplasm consists of mechanical cleansing of the esophagus by frequent irrigation. A Levine tube is passed to a point just above the neoplasm and through it warm saline or boric acid solution is flushed past the growth. If a gastrostomy is present, the washings will emerge in the stomach. If no gastrostomy has been performed, the washings either pass into the stomach or may be siphoned back. If these irrigations are repeated daily for four or five days prior to operation, a material change in the appearance of the ulcerating surface of the neoplasm will be noted.

A few authors have stressed the importance of pneumothorax before the operation in order to accustom the lung to the positive intrapleural pressure which takes place at the time of operation. I have never seen the need for this and have relied on my anesthetist to maintain varying degrees of positive intrapulmonary pressure. However, I can see no objection to preoperative pneumothorax provided that operation is not delayed too long. I do not subscribe to the recommendations of a few writers that the phrenic nerve be crushed either prior to or during the operation. Paralysis of the diaphragm adds another burden to an already handicapped patient in his effort to obtain maximum pulmonary ventilation.

#### GASTROSTOMY

If the neoplasm is located in the upper two thirds of the esophagus, a preliminary gastrostomy will be indicated.<sup>1</sup> Ten to fourteen days should elapse before resection of the organ is carried out. During this time, high caloric feedings containing all vitamins and minerals should be given through the gastrostomy opening. Marked improvement in the patient's general condition may be noted during this preparatory period, and there may be an appreciable gain in weight. The type of gastrostomy performed should be one that insures permanent patency at the cutaneous surface and one that is large enough to admit a no. 28 or a no. 30 French catheter. The Janeway gastrostomy meets these requirements but has the serious objection of frequent regurgitation of gastric contents through the opening. The valve gastrostomy described recently by Spivack apparently overcomes this deficiency. This procedure at present is the operation of choice.

If the carcinoma is located in the distal third of the organ, preliminary gastrostomy should not be carried out, because the presence of a gastrostomy will seriously interfere with the performance of an intrathoracic

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<sup>1</sup> Recently I have changed the plan of procedure just described. This was done in order to obviate regurgitation of gastric contents through the gastrostomy opening, which occurs even with the Spivack valvular gastrostomy. If the patient is in fairly good condition, a preliminary gastrostomy is not performed. Instead, during the thoracic part of the operation, the lower portion of the esophagus is divided about 2 inches (5 cm) above the cardia, and this lower 2 inch segment, still attached to the stomach, is dissected from the mediastinum and pushed into the abdomen. (It is covered with a rubber envelope to prevent contamination.) After completion of the thoracic procedure, the abdomen is opened through a small left rectus incision and the esophageal stump is brought out at the upper angle of the wound and sewn to the skin to form an esophagostomy opening. In this way the sphincter mechanism of the cardia is preserved and no leakage of gastric contents can take place. Another advantage of this new procedure is that the subsequent antethoracic esophagoplasty may be completed in one stage without fear of regurgitation of acid gastric secretion, which ordinarily causes digestion of the skin lined tube.

anastomosis between the stomach and the esophagus, the operation of choice for neoplasms in this situation. For the same reason it is questionable whether a jejunostomy should be performed for feeding purposes. However, an occasional patient may require such a procedure in order to improve the general condition. If it becomes necessary, an incision at the level of the umbilicus or below it should be used, in order to remove the field of this operation as far as possible from the upper part of the abdomen.

#### ANESTHESIA

In my experience, the combination of avertin with amylene hydrate and ethylene or cyclopropane anesthesia has been most satisfactory. Ethylene is the least irritating of the inhalation anesthetics and causes little or no circulatory depression. The only objection to its use is that the actual cautery cannot be used to divide the esophagus during the operation. However, its many advantages far outweigh this minor inconvenience. The anesthetic agent must be administered with varying degrees of positive pressure during the operation to influence the extent of inflation of the lung. Complete collapse of the lung should not be permitted to take place at any time during the operative procedure. During the course of the operation, perhaps every ten minutes, it is advisable to have the anesthetist expand the lung by increasing the pressure of the anesthetic gas. Any circulatory or respiratory depression that may have occurred is quickly overcome. It is important that the services of a competent anesthetist be obtained. The incidence of post-operative pulmonary complications depends in large measure on the skill of administration of the anesthetic agent.

A number of authors recommend intratracheal anesthesia, stating that the degree of inflation of the lungs can be more accurately controlled by this method. I have felt that the trauma of intubating the trachea in these frequently debilitated patients may well be a factor in the development of pulmonary complications and have therefore had no experience with this method for esophagectomy. The results with ordinary positive pressure anesthesia have been satisfactory.

It has seemed convenient, in discussing the operative treatment of carcinoma of the esophagus, to divide the organ into thirds. The upper third, extending from the hypopharynx to the arch of the aorta, presents an altogether different surgical problem from that encountered in the middle and lower thirds. The middle third of the organ extends from the arch of the aorta to a point about 34 to 36 cm from the upper incisor teeth. The length of this portion of the esophagus varies somewhat with the height of the patient. The lower third extends to the cardia. It becomes apparent that it is important for the esophagoscopist to determine accurately the position of the neoplasm with respect to the distance



the upper incisor teeth. This information helps the surgeon to decide which operative procedure he will choose.

#### CARCINOMA OF THE UPPER THIRD OF THE ESOPHAGUS

Surgical treatment of cancer of the hypopharyngeal, cervical and supra-aortic portions of the esophagus has been a difficult problem, owing mainly to the fact that tumors in these situations are frequently overlooked and reach the surgeon when growth has taken place beyond the wall of the organ. When the tumor is located in the cervical portion of the organ, the operative procedure employed will depend on the extent of involvement of the esophagus itself and also of neighboring structures, such as the larynx. Small tumors may be removed through lateral esophagotomy, with preservation of part of the circumference of the esophageal wall. Healing takes place by granulation with subsequent stricture, which will require dilations. If the larynx is involved also, laryngectomy in addition to cervical esophagectomy is indicated. This necessitates a permanent tracheotomy in the suprasternal notch and subsequent plastic reconstruction of the esophagus by the use of sliding cervical skin flaps (method of Eggers). In most of the reported cases the regional lymph nodes have been excised, but in most instances they were found uninvolved.

When the supra-aortic portion of the esophagus is involved by cancer, fixation to the trachea or to the main bronchus of the left lung may take place early in the course of the disease. For this reason, King advised that bronchoscopy be performed preoperatively in order to exclude such invasion. Infiltration of the left recurrent nerve is a not infrequent finding. Successful resections for cancer in this situation have been few. Kuttner freed a growth at the level of the clavicles and invaginated the lower stump, packing off the upper mediastinum. Zaaijer exposed this region by removing the manubrium, portions of the clavicle and the first two ribs on the left side, while Sauerbruch described a right anterior upper thoracic approach. The region under discussion may also be effectively exposed by an upper posterior mediastinotomy.

#### CARCINOMA OF THE MIDDLE THIRD OF THE ESOPHAGUS

Although a number of operations have been reported for malignant growths involving this portion of the esophagus, the procedure described by Torek has stood the test of time and experience. I have modified it in some respects in order to simplify the steps and shorten the operative time. The operation is based on the sound surgical principles of adequate exposure, free vision of the operative field and radical excision of the cancer-bearing focus with the associated lymph nodes.

As a result of some experimental and clinical studies, it has been determined that it is impossible to resect a portion of the thoracic part of the esophagus, perform an end to end anastomosis and obtain satisfactory union and continuity of the viscus. The reasons for this are 1 In order to effect a radical removal, too large a section of the organ would necessarily be removed to permit of bridging the gap without great tension at the subsequent suture line. 2 The esophagus is devoid of peritoneal covering, which is important in satisfactory healing. 3 The longitudinal muscle fibers surrounding the esophagus exert so strong a pull that any type of anastomosis is quickly torn apart.

The operation is tedious and difficult. The steps of the procedure should be carried out methodically, without haste. It is important to avoid unnecessary bleeding and to prevent infiltration of the mediastinum with blood. This requires careful hemostasis. The lobes of the lung should be handled as gently as possible, and care should be exercised not to traumatize the arch and the descending portion of the aorta. These precautions will have the effect of diminishing operative shock.

*Operative Technic*—The patient is placed on his right side with the head resting on the abducted right arm and his back close to the edge of the operating table. The left arm is elevated. One or two sandbags placed against the anterior region of the chest will prevent the patient from rolling forward on the operating table. After the usual preparation of the skin, the patient is draped in such a way as to leave exposed the chest, the upper part of the abdomen and the left shoulder and arm. The incision begins in the seventh interspace in the midclavicular line and is continued posteriorly along the course of the seventh interspace (fig 1). It is then carried upward between the vertebral border of the scapula and the spine as far as the third rib. The thoracic musculature is divided in the line of the cutaneous incision. All bleeding points are carefully ligated before the thoracic cavity is entered. An incision is made in the seventh interspace, dividing the parietal pleura with the intercostal muscles. The seventh, sixth, fifth and fourth ribs are quickly divided near the vertebral transverse processes, and the intercostal vessels are ligated with hemostatic sutures. A rib spreader is inserted, affording a clear view of the left thoracic cavity. The lobe of the lung usually collapse when the chest is opened, but complete collapse should not be permitted to take place. The arch and the descending aorta stand out in sharp relief. The esophagus lies to the right of the aorta, in the mediastinum.

A vertical incision is made in the mediastinal pleura from the lateral surface of the aortic arch down to the diaphragm (fig 2). The pleural edges are dissected away from the underlying esophagus. It is difficult to free the esophagus bluntly throughout its circumference at this point. A tape is placed around the organ at this site, and the

permits the surgeon to free the esophagus throughout its extent (fig 3) It is important to ligate the few small esophageal arteries rising from the aorta and to divide the small branches of the vagus nerve If

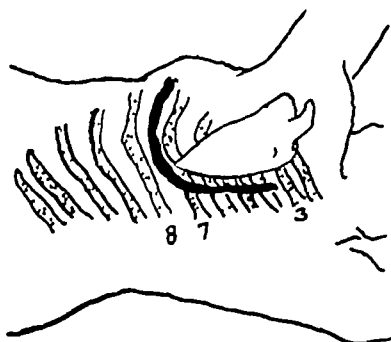


Fig 1—Incision is made in the seventh interspace, starting in the midclavicular line and carried posteriorly It extends upward between the vertebral border of the scapula and the spinal column The seventh, sixth, fifth and fourth ribs are divided about 1 inch (2.5 cm) lateral to the transverse vertebral processes

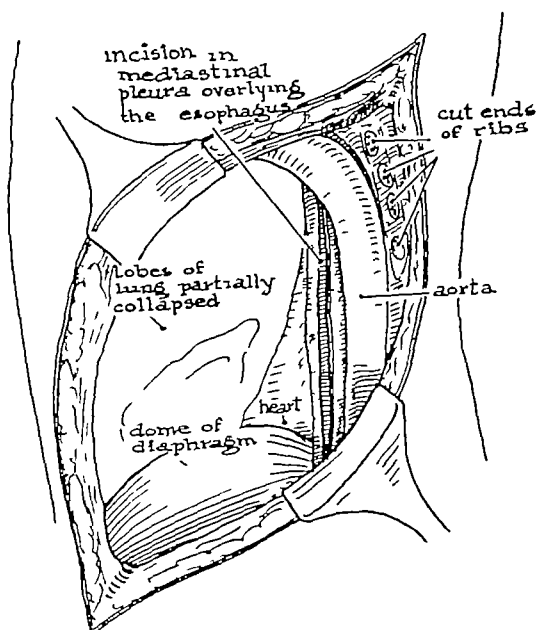


Fig 2—An incision is made in the infra-aortic mediastinal pleura, mesial to the aorta, in order to expose the esophagus

care is exercised in ligating all small vessels, there will be surprisingly little loss of blood The phrenic nerve is pushed to one side and usually remains out of the field of operation

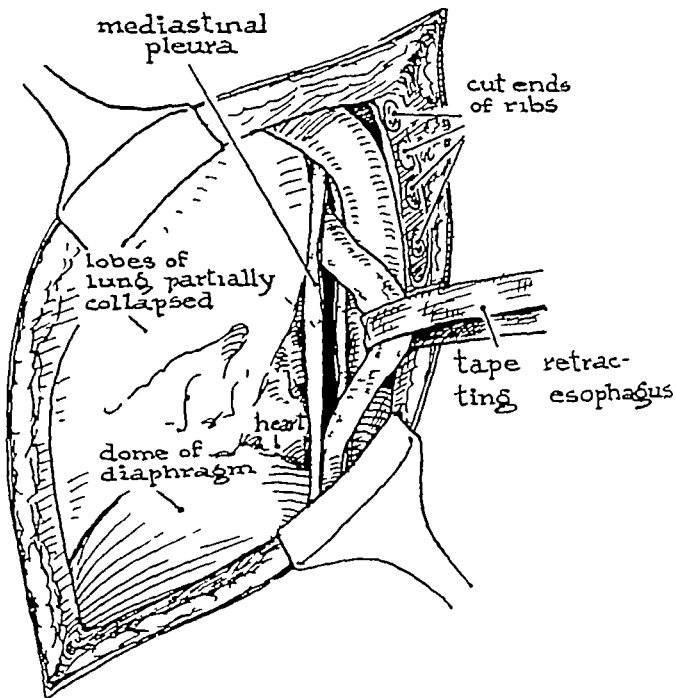


Fig 3—The esophagus is dissected from its attachment, and a tape is placed about it. Traction on the tape aids considerably in freeing the organ.

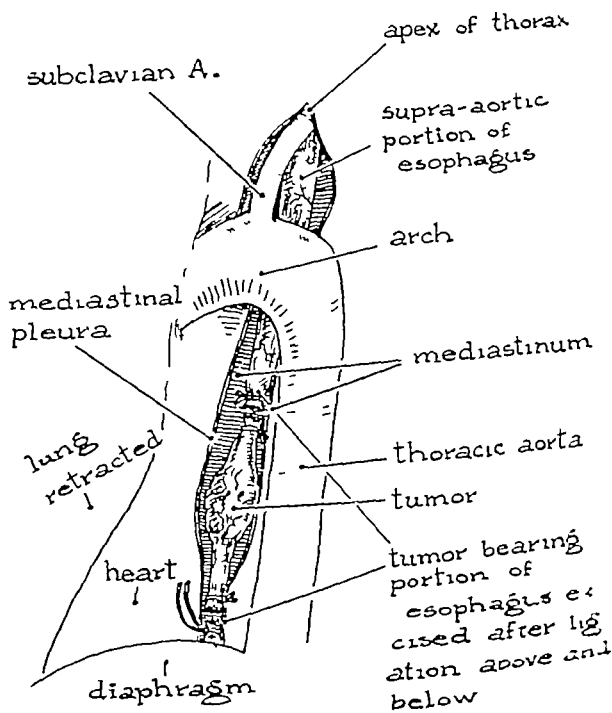


Fig 4—The mediastinal pleura above the arch is incised, and the esophagus is freed from the surrounding structures. The tumor-bearing portion of the esophagus, with a wide margin of normal tissue, is removed after double ligation above and below.

Figures 1 to 4 have previously appeared (*Surg, Gynec & Obst* 70 [Feb 15] 1940) and are reproduced by permission of the editors.

Unless the neoplasm is hopelessly attached to the aorta, the operation should be continued. Not infrequently the tumor may be fixed to the mediastinal pleura on the right side. In my first case this complication was present. It was found necessary to excise a piece of the right pleura together with the tumor in order to effect a radical removal. This resulted in a bilateral pneumothorax, but the effect on the patient was barely discernible. The opening in the pleura was packed and later closed with a running stitch of catgut.

An incision is made in the mediastinal pleura above the arch of the aorta and is extended as far as the apex of the thorax (fig 4). Pleural flaps are fashioned, and the underlying esophagus is freed from its surrounding attachments by careful finger dissection. The most shocking part of the operation occurs when the esophagus is separated from the posterior surface of the aortic arch. This maneuver must be executed with great care and with as little trauma as possible. The next step consists of division of the esophagus with the phenol cautery between heavy silk ligatures about 1 inch (2.5 cm.) above the diaphragm. The distal end is inverted into the stomach with two purse string sutures of silk. This may be reenforced by a layer of mattress sutures of chromic catgut. The esophagus is again divided between heavy silk ligatures above the neoplasm, and the tumor-bearing portion is removed (fig 4). This is an important modification of the original Torek technic. Removal of the tumor immediately eliminates the infected portion of the esophagus and decreases greatly the possibility of contamination of the pleural cavity. It also obviates dragging the tumor-bearing area through the thoracic aperture into the cervical wound.

In order to avoid further the possibility of pleural contamination, which would occur if the silk ligature accidentally slipped off the esophageal stump, a rubber condom is placed over the end of the organ and sewn into place with a few fine silk sutures. Another heavy silk ligature tied securely about the condom gives added security.

The remaining segment of esophagus is brought to a position above the aortic arch by means of a curved clamp placed from above downward behind the arch and grasping the ligature surrounding the cut end of the organ (fig 5).

After the esophageal stump has been brought to lie above the aortic arch, blunt dissection is continued into the root of the neck. The rubber-covered remains of the esophagus are then pushed upward into the neck, and the mediastinal pleura above the arch of the aorta is sutured to hold the organ in place (fig 6). The mediastinal pleura below the

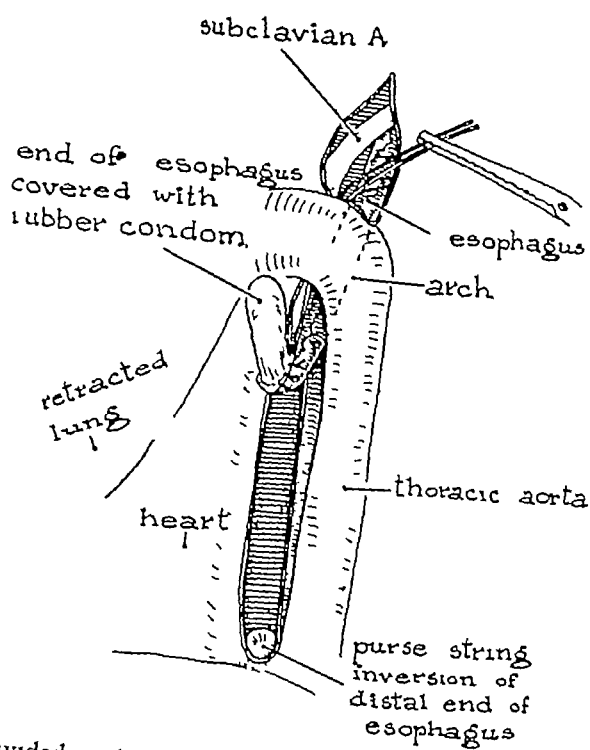


Fig 5—The divided end of the esophagus has been covered with a rubber condom, which is sutured to the esophageal wall. The distal end of the esophagus is inverted into the stomach. The mediastinal pleura is not sutured. The infra aortic portion of the esophagus is brought to lie above the arch.

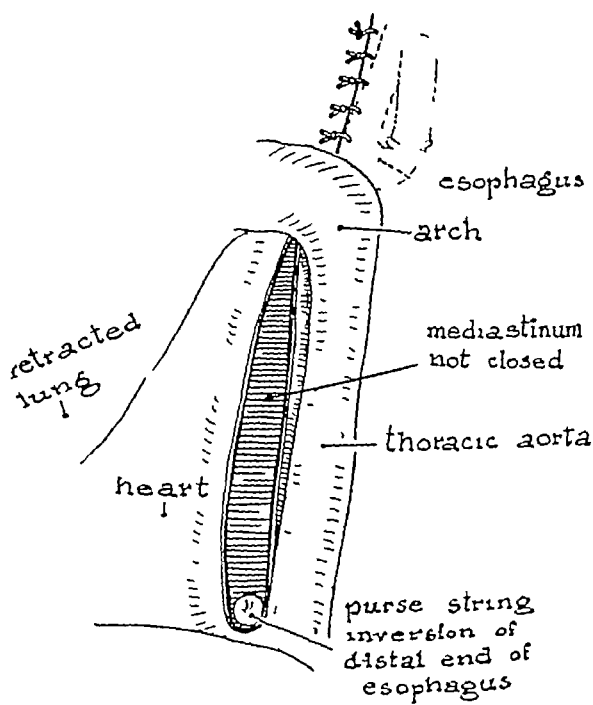


Fig 6—The mediastinum below the arch is left open to permit exit of the cellular tissues. The pleura above the arch is sutured in order to off the neck from the pleural cavity. The rubber-covered end of the esophagus has been pushed into the neck.

arch should be left open. Free drainage of the cellular tissues in the mediastinum is important, and this can be obtained by not suturing the pleural flaps.

It is important, especially when the mediastinum is left open, to drain the thoracic cavity. Many intrathoracic complications may develop, and it is a comfort to have a vent for the first five or six days. For this purpose a stab wound is made posteriorly in one of the lower intercostal spaces, and a medium-sized soft rubber tube is inserted. This should be fastened to the chest wall by means of a suture passed through a cuff. When the patient is returned to bed, the outer end of the tube should be placed under water in a bottle beside the bed, insuring a closed system.

The thoracic wound is now ready for closure. The ribs are approximated by passing heavy chromic gut sutures around the seventh and eighth ribs. The divided thoracic musculature is next repaired with interrupted sutures of plain catgut, and the skin is closed in the usual way. After the dressing is applied and the chest securely strapped, the anesthetist should inflate the lungs until air bubbles no longer appear at the outer end of the intercostal tube, which has been placed in a basin of water.

The patient is then turned on his back. The neck and the anterior region of the chest are exposed and prepared. A complete clean instrument tray should be at hand for this stage. Gowns and gloves should be changed. An incision is made along the anterior edge of the left sternocleidomastoid muscle. This structure and the great vessels are retracted externally. The lateral thyroid vein is ligated and divided, and the lobe of the thyroid is retracted mesially (fig 7). The cervical portion of the esophagus is easily identified and dissected free. A blunt hook is placed beneath it, and traction draws the remaining portion out of the root of the neck (fig 7). A subcutaneous channel  $1\frac{1}{2}$  inches (3.7 cm) in width is made, extending from the lower end of the cervical incision down to a point on the left side opposite the second rib (fig 8). A transverse incision  $1\frac{1}{2}$  inches in length is made at this site and the esophagus is drawn through this tunnel. It is wise to have the esophagus project beyond this incision for an inch or two, because some necrosis of the end of the organ may take place. The esophageal wall is sutured to the cutaneous incision with interrupted silk stitches. The cervical incision is closed air tight, and a dressing is applied (fig 9).

A word of warning about the blood supply of the esophageal stump is in order. This portion of the organ receives its nutrition from branches of the inferior thyroid artery. It is important, therefore, in conducting the cervical part of the operation, not to compromise the integrity of

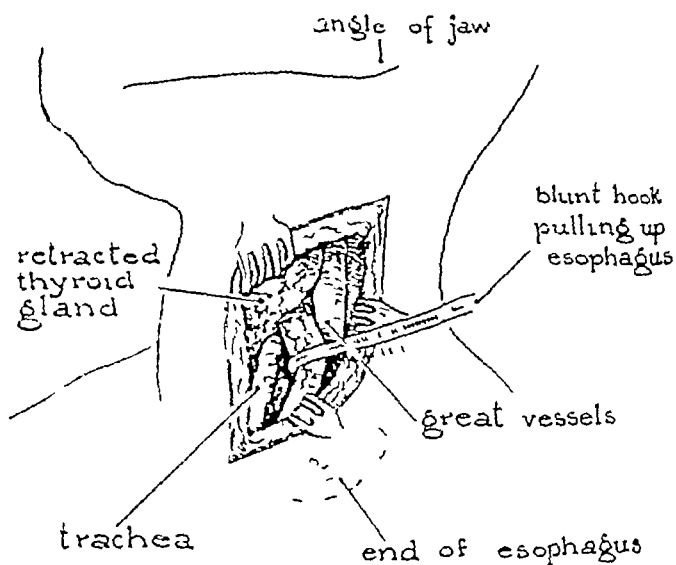


Fig 7—Second stage of the operation. The cervical portion of the esophagus is exposed, and the end of the organ, covered by the rubber envelope, as indicated in the dotted lines, is drawn out of the wound.

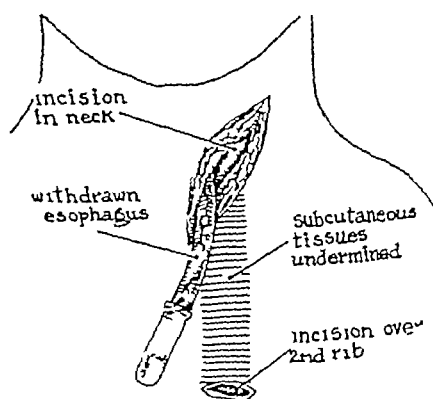


Fig 8—A subcutaneous channel is made, extending from the lower end of the cervical incision to about the region of the second rib.

this vessel. This requires careful retraction of the cervical incision, accurate hemostasis and the avoidance of rough blunt dissection.

The best insurance against shock on the operating table and also operatively, besides the already mentioned gentle operative technique, is a transfusion during the operation. To every patient operated on by me a transfusion of whole blood has been given on the operating table.



followed by a continuous intravenous drip of 5 per cent dextrose in saline solution. The latter should be continued postoperatively for two or three days. If the patient is elderly, edema of the lungs may develop if too much fluid is given by this method. The drip mechanism may be so regulated as to deliver to the patient between 2,000 and 3,000 cc of fluid in twenty-four hours.

When the patient is returned to bed, he should be placed in a semi-recumbent position. The Gatch bed is ideal for this purpose. Measures should be instituted to combat shock. Although hypodermic medication, stimulating enemas and external heat have undoubted value, the most effective remedy is a transfusion of whole blood. Sufficient morphine should be given to relieve pain. In recent cases I have placed the patient in an oxygen tent immediately after operation, and the patients so treated apparently have had less difficulty with breathing.

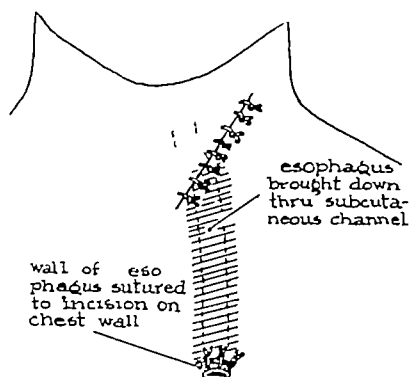


Fig 9—The esophagus is drawn through the channel so that its end projects beyond the cutaneous incision for a distance of 1 inch (2.5 cm). The incision is sutured to the wall of the esophagus with interrupted stitches of fine silk.

Figures 5 to 9 have been published previously (*Internat. Clin.*, vol. 1) and are reproduced by permission of the editors.

and fewer pulmonary complications. If inversion of the esophageal stump into the stomach has been satisfactory, fluid may be given by the gastrostomy tube. If inversion has not been satisfactory, it is wise to delay gastrostomy feeding until the sixth or seventh day. Regular feedings should be given as soon as the general condition of the patient permits.

The care of the esophageal stump is important. Beginning on the second day, the patient should be encouraged to swallow fluids, which must be caught in a basin. This cleanses the esophagus and helps to restore the act of deglutition. It is important to maintain good oral hygiene, and toward this end patients should be encouraged to chew gum.

The intrathoracic situation must be watched closely and may give the surgeon concern during the first week. Some indication of what is going on within the chest may be obtained from the temperature, the pulse rate, physical signs, roentgen examination of the chest and the amount and character of the material drained through the intercostal tube. If there is no dyspnea, if the temperature, pulse and physical signs are within normal limits and if the drainage diminishes each day, the tube may be removed permanently. If roentgen examination and the clinical course indicate the presence of empyema, surgical drainage will be indicated. It is important not to delay this step too long, because these patients, in view of their precarious condition, cannot stand infection for long.

The character of the material draining through the intercostal tube will indicate the progress of the intrathoracic situation. During the first two days the drainage is frankly sanguineous. After this period it gradually assumes a lighter color and decreases in amount until about the seventh or eighth day, when it usually stops completely. The tube may be removed soon afterward.

As soon as the patient's condition warrants it, usually about the end of the second week, the continuity of the esophagus should be established by inserting a rubber tube into the upper fistula and connecting it with the gastrostomy tube. The tube is held in place by carrying a tape around the patient's neck and attaching it to a safety pin which is inserted transversely into a rubber cuff placed about the tube about 2 inches (5 cm) below its upper end. The patient is then encouraged to take all nourishment by mouth. In order to swallow solid food, he must thoroughly masticate it and mix it with more fluid than does the normal person, so that it will descend more easily through the tube into the stomach. It is hardly necessary to add that the rubber esophagus should be removed frequently and cleansed.

The care of the patient subsequent to his discharge from the hospital is chiefly that of experimenting with various sizes of rubber tubing until the rubber esophagus fits snugly into the fistula above. Leakage of ingested fluid from the upper end may be obviated by having the patient compress the orifice against the rubber tubing.

If infection has not been a major issue in the patient's convalescence, rapid improvement will be noted. There will usually be a rapid gain in weight and strength. The question of connecting the esophageal fistula and the gastrostomy opening by an antethoracic esophagoplasty should not be considered until there is reasonable assurance that the cancer has been eradicated. In most instances at least two years must elapse before such reconstructive work can be undertaken.

It has been my experience that tumors located between the arch of the aorta and the left main bronchus offer the greatest technical dif-

difficulties. Fixation of the esophageal wall to either structure takes place early. Even though this fixation may be inflammatory in origin and not due to direct neoplastic extension, actual separation of the structures from each other constitutes a formidable and difficult procedure. Because it is impossible accurately to differentiate inflammatory from neoplastic fixation, the surgeon should not abandon the lesion as inoperable and should make every effort to separate the structures. At the same time, I must admit that the highest recurrence rate will be found in this particular group of cases. In the next case of this type that presents itself, I plan to insert radium at the time of operation in the hope of eradicating any remaining cancer cells. I have operated on 3 patients with carcinoma in this unfavorable location. One died of a recurrence in the superior mediastinum a little over two years later, the second succumbed to local recurrence and generalized metastases one year later, and the third is alive six months after operation.

Discussion of this subject is not complete unless mention is made of the so-called "pull-through" operation described by Denk and popularized by Turner. This consists of a blind tunneling out of the thoracic portion of the esophagus by the combined abdominocervical route. My objection to this operation is that it is a blind procedure and that the surgeon has no way of telling whether the lesion is operable except by the sense of touch. The chance of injury of adjacent structures is obviously very real. In fact, Turner himself, the operation's greatest proponent, discussed with some misgivings his difficulties, such as tearing of the growth, injury to the pleura and postoperative hemorrhage. It seems to me that adequate exposure with direct vision of the field of operation is a *sine qua non* for radical surgical treatment of cancer.

A number of surgeons, notably Abel, Lotheissen, O'Shaughnessy and Ricard and Ballivet, have recommended a transpleural approach on the right side, claiming that the operation is technically easier. In order to expose the esophagus completely by this route it is necessary to ligate and divide the azygos vein. I have practiced this operation on the cadaver and am not convinced that it is easier than the transpleural operation on the left already described. I agree with Torek that the liver, diaphragm and pericardium interfere with adequate removal of the esophagus below the growth and render satisfactory inversion of the lower end into the stomach very difficult.

*Carcinoma of the Lower Third of the Esophagus*—From the pathologic standpoint, cancers originating in the cardiac end of the stomach and secondarily involving the lower portion of the esophagus, that is, adenocarcinomas, should not be classed with the neoplasms originating in the esophagus itself, namely, the squamous cell tumors. The direction of lymphatic spread is quite different in each instance. Cancers

originating at the cardia spread to the gastrohepatic omentum and to the liver as well as to the mediastinum, often in the early stages of the disease, while esophageal tumors rarely extend to the lymph nodes below the diaphragm and remain purely local for some time. It will be seen, therefore, that carcinomas which arise from the esophageal mucosa will be more often amenable to resection. However, the same operation is applicable to cardiac carcinomas, if preliminary abdominal exploration indicates operability.

When the growth is located in the distal third of the organ, every effort should be made to reestablish continuity of the esophagus and the stomach by some form of anastomosis. The decision to elect this operative plan will rest on three factors: (1) an accurate interpretation of the extent and location of the growth in the roentgenogram, (2) histologic examination of the biopsy specimen (squamous cell carcinoma), and (3) the distance between the upper incisor teeth and the upper level of the tumor as determined by the esophagoscopist. Any tumor located 38 cm. or more from the upper incisor teeth may be considered suitable for this operation, all other factors being equal.

For this type of lesion I do not recommend preliminary gastrostomy, because the adhesions in the upper part of the abdomen produced thereby will seriously hamper the surgeon in mobilizing the stomach. If a preliminary jejunostomy for feeding purposes is necessary, it is suggested that it be placed below the umbilicus.

All the evidence to date indicates that transthoracic resection with esophagogastrostomy in one stage is the procedure of choice for carcinoma of the lower part of the esophagus. It is based on the sound surgical principles of free exposure, mobilization of the involved viscera, preservation of blood supply, radical excision of the cancer-bearing focus with its associated lymph nodes and physiologic restoration of esophagogastric continuity by a layer suture anastomosis.

The operation, a modification of the original Sauerbruch and Fischer procedure, consists of a transthoracic approach on the left side, incision of the diaphragm, mobilization of the upper two thirds of the stomach, resection of the tumor-bearing area, performance of a careful suture anastomosis between the end of the esophagus and the anterior wall of the stomach in two layers and telescoping of the esophagus into the stomach by drawing the latter organ upward in a sleeve-like manner around the esophagus in order to minimize any possible drag on the suture line.

*Operative Technic*—The details of the operation are as follows. The patient is placed on his right side with the head resting on an abducted right arm and his back close to the edge of the operating table. The incision begins in the eighth interspace in the anterior axillary line.

and is curved posteriorly, extending upward between the spine and the vertebral border of the scapula as far as the fourth rib (fig 10) The thoracic musculature is divided in the line of the cutaneous incision All bleeding points are carefully ligated before the thoracic cavity is entered An incision is made in the eighth interspace, dividing the parietal pleura with the intercostal muscles The eighth, seventh, sixth and fifth ribs are quickly divided near the spine, and the intercostal vessels are ligated with hemostatic sutures Use of a rib spreader gives excellent exposure of the left side of the thoracic cavity The inferior pulmonary ligament is divided, permitting collapse of the lower lobe Complete pulmonary collapse should not be permitted to take place This can be controlled by the anesthetist

The growth is then palpated Intimate fixation to the aorta or to the vertebral column renders the lesion inoperable A vertical incision is made in the mediastinal pleura, mesial to the aorta, from the arch down to the diaphragm (fig 11) The esophagus is identified and freed bluntly from the mediastinal tissues It is important to ligate the small esophageal vessels, but care should be taken not to jeopardize the blood supply of the esophageal stump to be utilized for the anastomosis Fixation to the right mediastinal pleura should not deter the surgeon I have encountered this complication on three occasions and have in each instance excised a portion of the right pleura in order to effect a radical removal The defect may be closed easily by utilizing the wall of the stomach after it has been mobilized

An incision is then made in the left leaf of the diaphragm, extending from the esophageal hiatus radially outward toward the ribs (fig 11) for a distance of 6 or 7 inches (15.2 to 17.7 cm) The esophagocardiac junction is freed bluntly from its loose attachment to the diaphragm The spleen and the fundus of the stomach quickly appear in the wound Judicious retraction of the edges of the diaphragmatic opening and insertion of gauze packs will expose adequately the proximal half of the stomach The left gastroepiploic vessels are ligated and divided, which permits the surgeon to enter the lesser sac By inserting the left hand in the lesser sac and drawing the stomach downward, it is not difficult to isolate the gastric artery near its origin and to divide it after careful double ligation Complete mobilization of the proximal half of the stomach is obtained after division of its ligamentous attachments at the upper part of the greater curvature The stomach may then be drawn up into the thoracic cavity with ease (fig 12)

During resection of the growth and the subsequent anastomosis, the entire thoracic cavity and wound must be protected from contamination Long rubber-covered clamps are placed on the stomach side beyond the growth in an oblique direction from the upper portion of the greater

curvature toward the lesser curvature, and the stomach is divided with the phenol cautery. The opening in the stomach is closed in two layers, silk being used and care taken to ligate separately all bleeding points (fig 13). A small rubber-covered noncrushing clamp is now placed

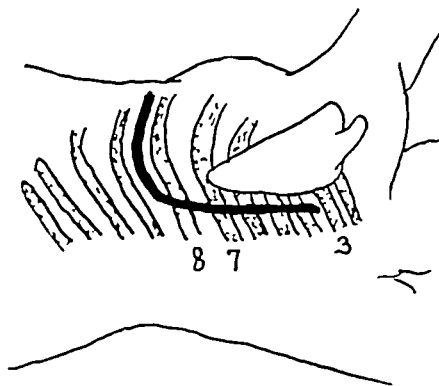


Fig 10—Resection and esophagogastrostomy. Incision is made in the eighth interspace. The eighth, seventh, sixth and fifth ribs are divided near the transverse vertebral processes.

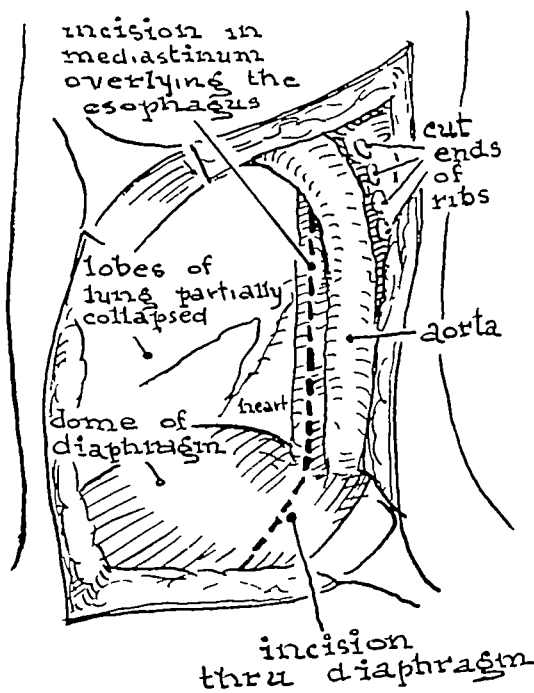


Fig 11—Incision is made in the mediastinal pleura. The diaphragm is split radially outward from the esophageal hiatus.

over the esophagus well above the tumor. A second crushing clamp is placed about  $\frac{3}{4}$  inch (1.9 cm) beyond this, and the esophagus is divided so as to leave at least  $\frac{1}{2}$  inch (1.2 cm) of the organ projecting beyond the rubber-covered clamp. The specimen is removed.

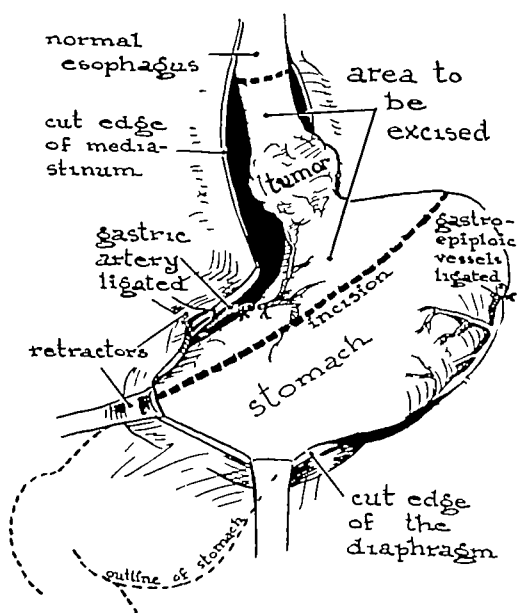


Fig 12—The tumor-bearing portion of the esophagus and the cardia have been separated from the mediastinum and the diaphragm. Mobilization of the stomach is accomplished by ligation and division of the gastric and left gastro-epiploic vessels.

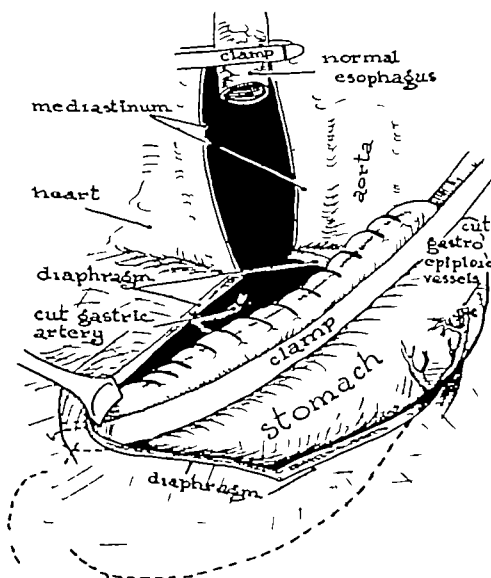


Fig 13—The stomach is resected in an oblique direction well beyond the growth and is closed with two layers of silk sutures. The esophagus is transected well above the cancer. A small rubber-covered clamp prevents soiling.

The upper end of the stomach in the region of the greater curvature is brought in approximation to the esophageal stump (fig 14). A two layer suture anastomosis, end to side, is next performed between the end of the esophagus and the anterior wall of the stomach at a point about 2 inches (5 cm) beyond its upper end (fig 15). The inner layer is a continuous Connell suture of fine silk uniting the mucosa and the submucosa. Every stitch must be correctly placed. It is important to avoid strangulation of the tissues. The second layer is a continuous or interrupted Lembert suture of fine silk, joining the muscularis of the esophagus to the muscle and peritoneal layers of the stomach. In order to protect the suture line from longitudinal tension, the stomach is drawn upward like a sleeve over the suture line and is anchored in this position by interrupted sutures of fine silk which include the muscularis of the esophagus and the cut edges of the mediastinal pleura (fig 16). The new anastomosis will usually be situated 1 or 2 inches (2.5 to 5 cm) below the arch of the aorta, and it will be seen that approximately one half of the stomach now occupies an intrathoracic position.

The radial incision in the diaphragm is then closed with interrupted sutures of silk, care being taken not to make the opening through which the stomach emerges too small. To prevent herniation of more stomach into the chest, the edges of the diaphragmatic opening are sutured to the wall of the stomach (fig 16). I cannot agree with Cattell and Marshall that it is imperative to crush the left phrenic nerve. In fact, I believe that there is real danger in this procedure. If the anastomosis has been made without tension, there need be no worry that it will be torn apart by movement of the diaphragm.

Through a small stab wound in the subjacent intercostal space a soft rubber tube is inserted for underwater drainage. The thoracic wound is then repaired in the usual manner by encircling the contiguous eighth and seventh ribs by heavy chromic sutures (fig 17). The thoracic musculature is carefully repaired by layer, and the skin is closed with silk. The anesthetist then inflates the lungs, thus helping the escape of air in the pleural cavity through the intercostal drainage tube, the end of which has been placed under water. A snug dressing is next applied to support the severed ribs. If the right pleural cavity has been opened, the right side of the chest must be aspirated at the completion of the operation.

It has been both surprising and gratifying to see patients go through this extensive procedure with little evidence of shock. The pulse rate has varied between 80 and 126. The blood pressure readings have shown very little variation, a slight drop occurring during ligation of the gastric artery and mobilization of the stomach. In the last 2 cases I have been able to complete the operation in two hours and five minutes.



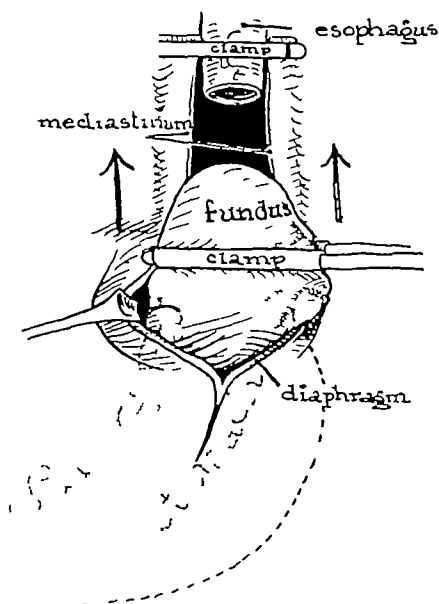


Fig 14—The stomach is drawn upward into the thoracic cavity and its upper end brought into position for anastomosis with the esophagus

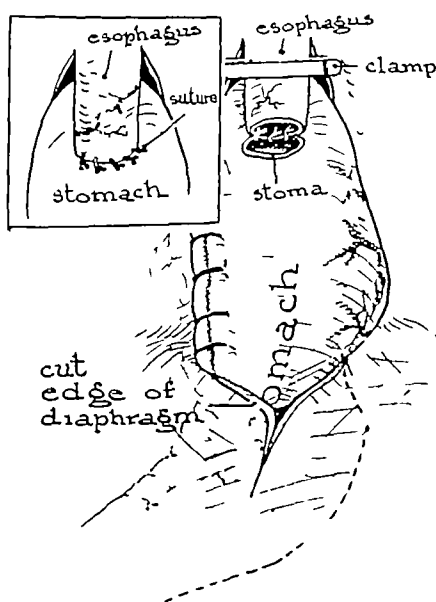


Fig 15—An end to side anastomosis in two layers is effected in the same manner as one performs gastroenterostomy. Silk sutures are used. Care should be taken to avoid strangulation of tissues. The insert shows the completed anastomosis.

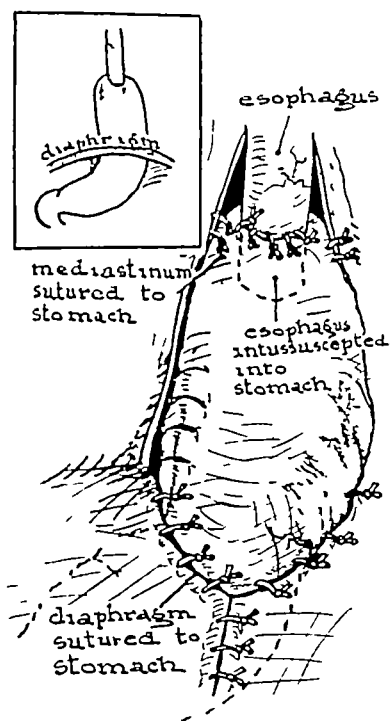


Fig 16—The esophagus is telescoped into the stomach by drawing the stomach upward in a sleevelike manner. To maintain this position, the stomach is tacked down to the esophagus and also to the mediastinal pleura with interrupted stitches of silk. The remainder of the mediastinum is left open. The opening in the diaphragm is partly closed, the remaining edges being sutured to the wall of the stomach in order to prevent herniation.

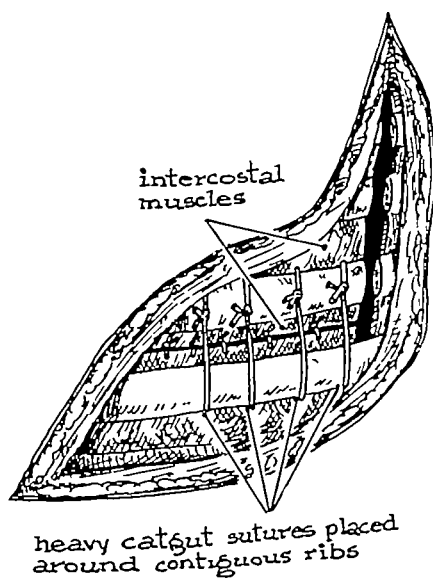


Fig 17—The thoracic wound is closed by encircling the contiguous eighth and ninth ribs with heavy catgut sutures.

Figures 10 to 17 have appeared previously (*Surg, Gynec & Obst.* 70 : 559 [Feb 15] 1940) and are reproduced by permission of the editors.

## POSTOPERATIVE CARE

Before undertaking this operation, it is most important to explain to the patient that he must not swallow for five or six days. The processes of repair at the suture line will be hastened by full cooperation of the patient in this respect. To supply fluids, use is made of the continuous intravenous drip of 5 per cent dextrose in physiologic solution of sodium chloride. It may be necessary to give another transfusion during the first day or two.

Small sips of water may be given on the fifth or sixth day. If nothing appears through the drainage tube, it is assumed that the suture line has healed and is intact. Increasing amounts of liquid are not given until about the sixteenth day, when custards, jellies, cereals, etc., are permitted. The diet is rapidly increased thereafter. Solid food should not be given until the third or fourth week.

The lumen at the site of anastomosis may diminish in caliber during the succeeding two or three months. If this happens, bougienage through an esophagoscope will become necessary. Such treatment should not be undertaken until there is reasonable assurance that the repair at the site of anastomosis is solid.

## RESULTS

Up to the time of writing I have operated on 17 patients with carcinoma of the esophagus. Of this group, 6 were found to be inoperable, and 11 were treated by radical resection. The operability percentage was 64.7. In the group of 11 patients subjected to resection, 3 died postoperatively, a mortality of 27.2 per cent. One patient died of a tension pneumothorax on the right side. I believe that this death was due to an error in judgment and could have been prevented. The second patient died of a cerebral hemorrhage resulting in hemiplegia seventy-two hours after operation. At autopsy the intrathoracic situation was found to be satisfactory, and the anastomosis between the stomach and the esophagus was intact. There was no evidence of infection. The third patient, a physician of 54, died twelve hours after operation, of shock. The tumor in this instance was firmly attached to the diaphragm and the right pleura. The operation was unusually difficult and consumed almost four hours. Autopsy was not permitted.

In 7 of these cases the modified Torek operation was performed, with 1 death. In the remaining 4, resection with intrathoracic esophago-gastrostomy was carried out. There were 2 deaths. The late results in the patients who survived operation are of considerable importance. Of the 8 survivors, 1 died of a recurrence in the superior mediastinum twenty-three months later, 1 died of coronary disease after three months, and 1 died of generalized metastases one year after operation. The 5

survivors are alive and well three and a half years, eleven months, seven months, six months and 1 month respectively after operation. In the second and third cases resection with esophagogastrostomy was performed.

In addition to the aforementioned group, I have operated on 10 additional patients with carcinoma of the cardia secondarily involving the lower part of the esophagus. Three of these were found to be operable, an operability rate of 30 per cent. In these 3 patients transthoracic resection with esophagogastrostomy was performed. There were 2 post-operative deaths. One patient, a woman of 72, in only fair condition, seemed slowly to disintegrate during the following three days. At postmortem examination the cause of death was not demonstrable. The suture line was intact, and there was no evidence of infection. The second patient died suddenly of a cerebral embolus on the third day. At autopsy the anastomosis was found to be intact, and there was no infection. The third patient is alive and well eight months after the operation. The cases comprising this group will form the basis of a subsequent paper.

In the group with cardiac carcinoma it is important to find out whether the growth is resectable before opening the chest. The rapidity of growth of these tumors and the high incidence of inoperable lesions when the patients first consult the surgeon make this precaution advisable. Preliminary exploration of the upper part of the abdomen through a small left rectus incision will demonstrate the presence or absence of metastases to the liver, involvement of the lymph nodes and fixation of the growth to the surrounding structures. If the tumor seems operable, the chest may be opened and resection carried out. If inoperability is demonstrated, the incision is closed, or, if obstruction is a prominent factor, gastrostomy may be performed. By this plan an unnecessarily high mortality in the inoperable group will be avoided.

Rapid progress is being made in the surgical treatment of cancer of the esophagus, a disease considered until recently as hopeless. It is my firm conviction that in the near future surgical treatment will be the generally accepted method of handling this disease.

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# MALIGNANT TUMORS OF HERNIAL SACS

LEO M. ZIMMERMAN, M.D.

AND

HAROLD LAUFMAN, M.D.

CHICAGO

The sacs of inguinal hernias have been known to contain almost every type of normal and diseased abdominal viscus. Malignant tumors of organs contained in the sacs have been described, and, less frequently, secondary involvement of the tissues of the sac by extension or metastasis has been noted. Primary malignant tumors of the tissues of hernial sacs, however, are extremely infrequent. Barcz<sup>1</sup> reported an adenocarcinoma of a hernial sac, but it is obvious that a tumor of this type could not have arisen primarily from any but an epithelial structure and could not, therefore, have been primary in the sac. Unfortunately, postmortem examination was not done. Pagliani<sup>2</sup> reported a benign tumor, a fibromyxoma, which was primarily in the sac and which had been diagnosed preoperatively as a strangulated hernia. The only case encountered in the literature of the past two decades of primary malignant tumor of the sac of an inguinal hernia was cited by Richard<sup>3</sup> from a dissertation by Roessle, in which postmortem examination disclosed a fist-sized tumor of a hernial sac with metastases to the inguinal and para-aortic lymph nodes and in which a diagnosis of malignant mesothelioma was made.

Because of the rarity of malignant neoplasms involving hernial sacs, we are briefly reporting 3 cases, in 1 of which we have complete data, including postmortem observations. In the other 2 cases, while a diagnosis of malignant mesodermal tumor of the excised sac tissues was made, the data are somewhat equivocal. One of the patients is still alive and free from recurrence, and in the case of the other permission for autopsy could not be obtained. Each of these patients presented a different type of tumor, but all the growths were sarcomas, that is, were malignant neoplasms of mesodermal structure. All were rather bizarre forms, and positive histologic identification was difficult.

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From the Departments of Surgery of the Michael Reese Hospital and the Chicago Memorial Hospital.

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- 2 Pagliani, F. Tumore del sacco erniario. *Bull d sc med, Polona* 109: 108-119, 1937.
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In each of the cases to be described the patient was operated on with a diagnosis of incarcerated inguinal hernia, and the presence of a malignant growth was not suspected until microscopic examination of the excised sac tissues was made. It must be understood that hernial sacs consist of peritoneum and subperitoneal areolar tissue. These layers are continuous with analogous layers of the abdominal wall. In 2 of these cases the malignant process was more or less diffuse, there is no way of knowing specifically in which portion of these layers the tumors arose, and we do not contend that they necessarily involved the hernial tissues first. The tumor in the third case was apparently limited to the sac of the hernia.

#### REPORT OF CASES

CASE 1—R P, a boy 11 weeks old, was admitted to the Michael Reese Hospital on Sept 5, 1938, with a diagnosis of strangulated left inguinal hernia. The scrotal swelling had been present for eight days, and vomiting, restlessness and abdominal distention had been noted intermittently for four days. On the day of admission an attempt had been made to reduce the hernia, and the child had gone into shock.

Because of a tense, fluctuant swelling in the left side of the scrotum, which extended up into the inguinal region, and abdominal distention, operation was done. Inguinal incision disclosed a thickened and edematous hernial sac which was filled with fluid, but contained no viscus. As the ring was widened, there was a profuse flow of clear, straw-colored ascitic fluid from within the abdomen. Because the fluid was not bloody, laparotomy for possible reduced gangrenous bowel was not done. The sac was removed and the ring closed.

The immediate postoperative course was satisfactory. Subsequently a febrile course supervened, which subsided with the drainage of clear ascitic fluid between the sutures of the inguinal incision. The pathologist's diagnosis, returned at that time, was highly malignant tumor of mesenchymal origin. The fever recurred on the seventh postoperative day, and the course was then progressively downhill until death occurred, on the ninth day after operation.

Autopsy observations were relatively meager. There was fluid in the abdomen and in both pleural cavities, compressing the lungs. Scattered, flat elevations were seen distributed over the intestine and on the pleural surface of the diaphragm. There was, curiously, no other involvement of the parietal peritoneum than that of the hernial sac. When sectioned, the infiltrations were just beneath the serosal surfaces and did not involve the deeper layers of the intestinal wall.

Microscopic examination of the excised hernial sac, as well as of the serosal plaques and mesenteric lymph nodes, revealed large cells with distinct vesicular nuclei, each containing a clearcut nucleolus. Occasional giant cells were seen (fig 1). The pathologist's diagnosis was primary peritoneal malignant tumor, a so-called mesothelioma of the peritoneum.

CASE 2—M M, a 64 year old white man, was operated on on Feb 6, 1939, because of a right inguinal hernia which had been present for twenty years. For the past three months there had been symptoms of incomplete intestinal obstruction and considerable loss of weight. The patient had attempted to wear a truss, but as the hernia was irreducible the truss merely aggravated the pain.

At operation the sac was greatly thickened and infiltrated and was firmly adherent to the contained intestine. The bowel and its mesentery were greatly thickened, and the serosal surfaces were roughened. There were numerous transparent nodules on the surface which appeared to consist of inspissated fibrin. As the internal ring was dilated, a generous flow of ascitic fluid from the abdominal cavity appeared. A finger inserted into the peritoneal cavity encountered nodularity of the serosal surfaces comparable to that present in the sac.

The bowel was freed from the sac and reduced. At one point the adhesion was so dense that separation seemed perilous, and a button of thickened sac was left attached to the surface of the bowel. The remainder of the sac was removed and the canal repaired. The postoperative course was uneventful.



Fig 1—Metastasis to a lymph node. The section contains many lymphocytes which are part of the normal lymph node and an infiltration of large cells showing a distinct vesicular nucleus with a clearcut nucleolus. These cells are seen in the marginal sinus and invade the lymph node proper. Occasionally a multinucleated giant cell is seen. [Note: The primary tumor apparently arose in the peritoneum, a so-called mesothelioma of the peritoneum.]

Rather to our consternation, the pathologist again reported a malignant tumor. At first this was thought to be metastatic from the colon because of the presence of mucoid cells, but subsequent detailed study indicated that the growth was probably a malignant tumor of mesodermal origin, and a presumptive diagnosis of liposarcoma was made. The patient failed rapidly despite palliative irradiation and died six months after operation. Unfortunately, consent for autopsy could not be obtained.



Fig 2—Accumulations of large cells arranged in groups. Many of the cells show a signet-shaped nucleus and a lightly staining (empty) cytoplasm. These cells invade the tissue. This was probably a very malignant liposarcoma. However, the possibility of its being part of metastatic mucinous adenocarcinoma of the large intestine could not be ruled out.



Fig 3—Degenerated connective tissue fibers separated by large empty spaces with very few cellular elements in this region. The periphery shows a rather rich infiltration with lymphocytes. It is possible that this was a connective tissue tumor of the type of a fibromyxosarcoma. It is not likely that the empty spaces consisted of a foreign body of the type of paraffin, though that must be taken into consideration. There was no evidence of epithelial structures in this tissue.

The pathologist's report stated "The tissue is invaded by accumulations of large cells which are arranged in groups. Many of the cells have signet-shaped nuclei and a lightly staining or empty cytoplasm. This is probably a very malignant liposarcoma. However, the possibility of its being part of a metastatic mucinous adenocarcinoma of the large intestine cannot be ruled out" (fig 2).

**CASE 3**—This case is included in this report through the courtesy of Dr Harry Stimson, who operated on the patient, a 60 year old man, on Feb 21, 1939, at the Chicago Memorial Hospital, because of an incarcerated left inguinal hernia of about two weeks' duration. The sac was found to be of the indirect type and was attached to the cord. Its walls were thick and edematous. The changes were limited to the tissues of the sac of the hernia and stopped abruptly at the internal ring. The sac was excised and the hernia repaired. The patient had an uneventful postoperative course and was entirely well when last seen, ten months after the operation.

*Pathologic Examination*—The excised sac was composed of amber, friable tissue which in areas was dark red and lobulated. On section, gelatinous and hemorrhagic material exuded from the surface. In many features the tissue resembled degenerated thyroid gland. Microscopically it had the appearance of a degenerated fibromyxoma or a fibromyxosarcoma with much subacute and chronic granulation tissue (fig 3).

#### COMMENT

Three cases are reported of malignant tumors involving the sacs of indirect inguinal hernias. All the patients were operated on with a diagnosis of incarcerated hernia, and the presence of a malignant neoplasm was not suspected until histologic study of the excised sac tissues was made. The tumors differed in each case, and all were rather bizarre and difficult of positive histologic identification. In the first case described the patient was an infant, and the tumor was an embryonic type of growth, a mesothelioma of the peritoneum, which was diffuse and involved the subserosal layers of the peritoneum and the pleural diaphragm. It probably originated in multiple centers. Strangely, the only portion of parietal peritoneum involved was the excised portion of the hernial sac. It is likely that ascites resulted from the presence of the tumor, and the appearance of the hernia was due to distention of the sac by ascitic fluid.

The data concerning the other 2 cases are less complete. In the second there was a rather diffuse tumor which involved the abdominal as well as the hernial portions of the wall. It was probably liposarcomatous, although the possibility of its being a metastatic epithelial growth could not be positively ruled out. In the third case a fibromyxosarcoma of the tissues of the hernial sac was present, it was of decidedly lower malignancy and was apparently confined to the tissues of the sac. The patient was well and free from recurrences when last heard from, ten months after the operation.

# CONGENITAL ABSENCE OF THE SACRUM

I M ZELIGS, M D

IOWA CITY

## INCIDENCE

Congenital absence of the sacrum, either partial or complete, is of relatively infrequent occurrence. Hamsa,<sup>1</sup> in 1935, could find but 18 cases in the literature. In his review of the subject he included a synopsis of each of these cases and added 2 others. Girard,<sup>2</sup> in the same year, found 7 other cases in the literature and reported 1 of his own. Since that time 11 additional cases have been reported.<sup>3</sup>

## ETIOLOGY

There are several etiologic theories. Friedel<sup>4</sup> stated the belief that caudal suppression results from minute embryonal trauma. Wertheim<sup>5</sup> expressed belief in a late prenatal origin. Hamsa<sup>1</sup> stated that the hypothesis of Feller and Sternberg<sup>6</sup> is most plausible, "which explains the sacral variations and peripheral manifestations on the basis of a varying degree of defects in the posterior portions of the metameric segments,

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From the Department of Orthopedic Surgery (service of Dr. Arthur Steindler), State University of Iowa Hospitals.

1 Hamsa, W. R. Congenital Absence of the Sacrum, *Arch Surg* 30:67 (April) 1935.

2 Girard, P. M. Congenital Absence of the Sacrum, *J Bone & Joint Surg* 17:1062 (Oct) 1935.

3 (a) Araújo, A. Distrofia cruro-vesico-glútea por agenesia total do sacro-coccyx, *Arq brasil de cir e ortop* 4:43 (Sept-Dec.) 1936. (b) Barros Lima A. proposito de um caso de malformação do sacro, *ibid* 3:195 (Dec) 1935. (c) Diaz Lira, E. Agenesia sacrococcigea, *Rev ortop y traumatol* 7:231 (Jan) 1938. (d) Guilleminet, M. Agénésie subtotale du sacrum et du coccyx, *Lyon chir* 35:369 (May-June) 1938. (e) Hilgenreiner, H. Ein Fall von Anchypodie, *Ztschr f Orthop* 66:224, 1937. (f) Kienbock, R., and Zimmer, A. Angeborener partieller Kreuz- und Steissbeindefekt, *Röntgenpraxis* 7:111 (Feb) 1935. (g) Lamont and Graux. Agenesie sacro-coccygienne, *Echo med du Nord* 5:88 (Jan. 19) 1936. (h) Müller, J. H. Ein Fall von Aplasie des Sacrum, *Röntgenpraxis* 8:105 (Feb.) 1936. (i) Pouzet, F. Les anomalies de développement du sacrum, *Lyon chir* 35:371 (May-June) 1938. (j) Willemin, F. Spondyloptose par agénésie de la base sacrée, *J de radiol et d'electrol* 21:57 (Feb) 1937.

4 Friedel, G. Defekt der Wirbelsäule vom 10. Brustwirbel an abwärts bei einem Neugeborenen, *Arch f klin Chir* 93:944, 1910.

5 Wertheim, C. C. Vollständiger Mangel des Kreuz- und Steissbeins bei einem Neugeborenen, *Monatschr f Geburtsh u Frauenkr* 9:127, 1857.

6 Feller, A., and Sternberg, H. Zur Kenntnis der Fehlbildungen der Wirbelsäule, *Virchows Arch f path Anat* 280:649, 1931.



with additional involvement of the anterior portions in cases with abdominal visceral anomalies." Whatever the true mechanism is, the condition undoubtedly dates back to early embryonal life. As with other manifestations of suppression, as well as with errors of differentiation, the neurologic and the local variations occur simultaneously.

#### COMPATIBILITY WITH LIFE

This depends usually on the extensiveness of associated anomalies. When visceral malformations are absent and other significant developmental aberrations are minimal, life is usually possible.

#### CLINICAL FEATURES

The characteristic clinical features are, in part, manifestations of the vertebral defect and, in part, manifestations of the neurologic lesion which almost inevitably accompanies it. Examples of the former are (1) a flattening replacing the normal convexity of the sacrococcygeal region, (2) flattening of the buttocks, (3) shortening of the intergluteal fold, and (4) absence of the bony concavity of the sacrococcyx normally palpable on rectal examination.

The neurologic features result from involvement of the sacral or the lumbosacral plexus and include to a varying degree (1) incontinence of urine and feces, (2) atrophy and diminished muscle power of the lower extremities, and (3) associated deformities of the feet.

The atrophy is frequently more marked below than above the knee, as was pointed out by Hilgenreiner,<sup>30</sup> with a resultant cone-shaped appearance to the extremities. Such a condition is often referred to as the "sirene" or "mermaid" type. The patient may or may not have adequate muscle power to stand or walk. This frequently depends on the associated congenital deformities. Such deformities are frequent and include

1 Deformities of the feet. These are present in the great majority of cases. The deformity usually takes the form of paralytic clubfeet. In a number of cases there are equinovarus of one foot and calcaneovalgus of the other. Other deformities have been reported. In the case of Barros Lima<sup>31</sup> there were marked external rotation deformities of both feet. The patient of de Araujo<sup>32</sup> showed bilateral ankle valgus, rocker-bottom feet and congenitally short metatarsal bones.

2 Anomalies of other parts of the vertebral portion of the spine. These are also frequently associated conditions. They include suppression of more cranial segments (Friedel<sup>1</sup> White<sup>2</sup>), hemivertebrae (de Araujo<sup>32</sup>), failure of development of neural arches (Hilgenre-

<sup>7</sup> White C. A Fetus with Congenital Absence of the Sacrum. *Proc Roy Soc Med* 4: 279, 1911.

reiner<sup>3c</sup>), sacralized and wedged fifth lumbar vertebra (Kienbock and Zimmer<sup>3d</sup>), and congenital aplasia of articular apophyses (Diaz Lira<sup>3e</sup>)

3 Dislocation of the hips This condition has been reported in a number of cases<sup>8</sup> It is attributed to the decreased transverse diameter of the pelvis and the almost vertical iliac wings

Among the deformities occurring less frequently are congenital scoliosis (as in 1 case reported here), genu recurvatum,<sup>8</sup> congenital subluxation of the knee<sup>3e</sup>, congenital synostosis of several ribs, and certain urogenital malformations, such as urethrovaginal fistula or anal atresia (Feller and Sternberg<sup>6</sup>)

Sensory disturbances in the distribution of the lumbar or the lumbosacral plexus occur but do not necessarily parallel the motor changes either in distribution or in severity In many cases sensory involvement could not be accurately determined owing to the age of the patient

#### CLASSIFICATION

Foix and Hillemand<sup>9</sup> have classified the condition according to the extensiveness of involvement of the lower portion of the cord and the vertebral segments into four types

1 Complete sacrococcygeal agenesis The sphincters, buttocks and lower extremities are almost always involved The ilia are frequently approximated posteriorly, with a decrease in the transverse diameter of the pelvic ring Associated congenital malformations are common and, if extensive, may be incompatible with life Roentgen examination reveals complete absence of the sacrococcyx

2 Subtotal sacrococcygeal agenesis The coccyx and the last few sacral segments are absent The sphincters, buttocks and lower extremities are involved, and the pelvis is somewhat narrowed It was for this type that Foix and Hillemand,<sup>9</sup> considering the clinical picture to be a syndrome, introduced the term "dystrophie cruro-vesico-fessiere" The associated congenital conditions are usually less extensive than with type 1

3 Absence of the lateral half of the sacrum In this group there are modifications or absence of the sacral wings and univertebral or multivertebral hemiatrophy There are usually no associated symptoms

4 Total or partial agenesis of the coccyx There are usually no symptoms, and the diagnosis is usually made roentgenologically

The great majority of anomalies reported are of the first two types The incidence of types 3 and 4 cannot well be determined, since these types are usually asymptomatic and are rarely reported There are, however, several reports<sup>10</sup>

8 Hamsa<sup>1</sup> Hilgenreiner<sup>3a</sup>

9 Foix, C, and Hillemand, P Dystrophie cruro-vesico-fessiere par agénésie sacro-coccygienne, Rev neurol 31 450 (Nov) 1924

## REPORT OF CASES

The files of this clinic reveal 4 cases on record

CASE 1—V F, a girl aged 5 years, has been followed at the clinic since the age of 9 months. She was the sixth child and was born of breech delivery with difficult labor. One sibling, the third child, died of a meningocele. The mother's sister and the father's brother each have a child with congenital clubfeet. The patient has had complete urinary and rectal incontinence since birth.

Physical examination revealed the head, neck, thorax and upper extremities to be normal. The lower extremities were underdeveloped, with moderate atrophy of the calves and, to a lesser extent, of the thighs. There was absence of the

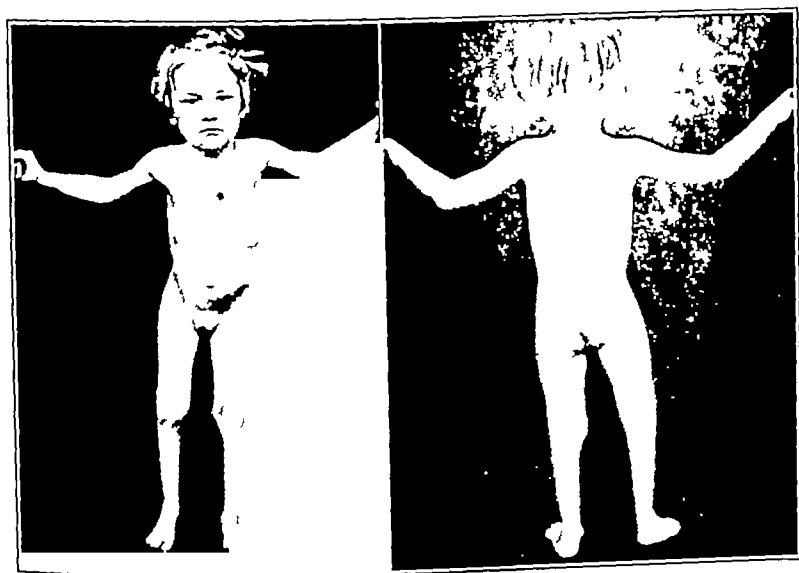


Fig 1 (case 1)—Flattening of the buttocks, shortening of the intergluteal fold, moderate atrophy of the calves and, to a lesser extent, of the thighs, and mild congenital scoliosis. The clubfeet have been almost fully corrected.

roundness of the sacrococcygeal region and flattening of the buttocks with shortening of the intergluteal fold (fig 1). There was a suggestion of cone-shaped tapering of both lower extremities. The muscle power of these extremities was moderately impaired, but the child could stand and walk fairly well without support. There were bilateral clubfeet, equinovarus on the right and calcaneovalgus on the left. There was partial paralysis of the long extensor muscle of the great toe on the right and of the common extensor muscle of the toes on the left. Sensation was intact. The deep reflexes of the lower extremities were normal. There was a mild 'upper right dorsal, lower left dorsal and right lumbar' scoliosis (fig 3). There was moderate diastasis recti, with slight abdominal

10 Froelich. Absence congénitale d'une moitié du sacrum. *Rev. med. de la t*  
37 308, 1905. Leri, A., Pettidi and Cottenot. Anomalie du sacrum, *Bull. et mem.*  
*Soc. med. d'hop. de Paris* 48 1173 (July 18) 1924.

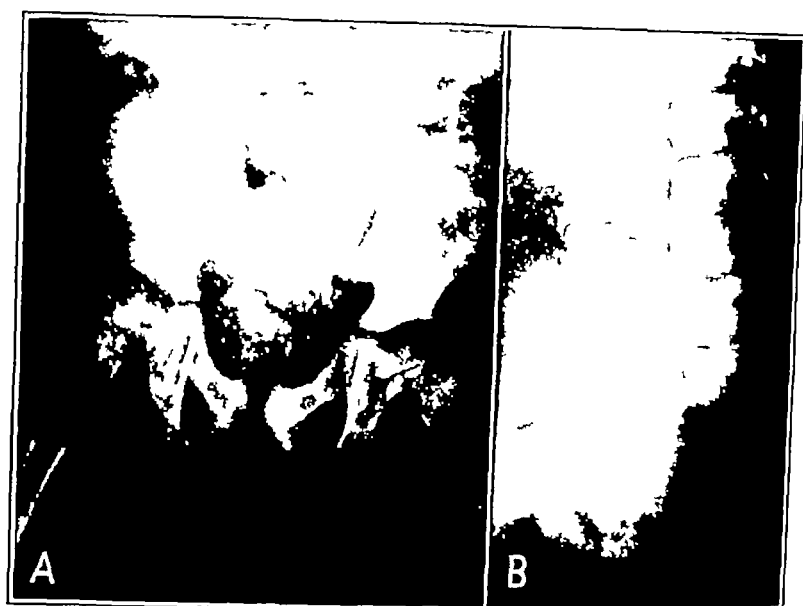


Fig 2 (case 1) — *A*, malformation of the second sacral vertebral body, with deviation to the right and absence of the sacrococcyx below this level *B*, lateral view, showing absence of the sacrococcyx below the level of the second sacral vertebra



Fig 3 (case 1) — Hemivertebrae in the dorsal part of the spine, with associated scoliosis, spina bifida in the lower dorsal region, six lumbar vertebrae and four sacral vertebrae, and synostosis of the first and second ribs posteriorly on the right (1)

protrusion. Rectal examination revealed poor sphincter tone. Soft tissue was encountered instead of the normal bony concavity of the lower part of the sacrococcyx. There was a congenital malformation of the urethra which opened into the vagina, being separated from the latter by only a thin septum. Partial anal atresia had been noted during infancy and had yielded satisfactorily to digital dilations.

Roentgen examination revealed the following abnormalities:

- 1 Clubfeet and scoliosis, as described
- 2 Congenital partial synostosis of the first and second ribs posteriorly on the right (*A*, fig 3)
- 3 Congenital malformation with hemivertebrae from the third to the tenth dorsal vertebra, with spina bifida occulta in the lower part of the dorsal region (fig 3)
- 4 Six lumbar vertebrae (fig 3)



Fig 4 (case 2)—Absence of the roundness of the sacrococcygeal region, some shortening of the intergluteal fold, tapering of the lower extremities and excoriations and pustules of the buttocks. The clubfeet have been almost fully corrected.

- 5 Malformation of the second sacral vertebral body with deviation to the right (fig 2*A*)

- 6 Absence of the sacrococcyx below this level (figs 2*A* and *B*)

Treatment was designed toward correction of the clubfeet by the usual orthopedic measures. A Brockman operation was necessary on the right side, from which the patient is now convalescing. The child has been equipped with a brace for the left foot. In the past few years she has had several attacks of pyelitis and suppurative otitis media and a number of fecal impactions, from which she has made, however, uneventful recoveries.

CASE 2—R. M. S., a girl aged 7 months entered the clinic at the age of 4 months for clubfeet. She was the fourth child. She was delivered at home at

full term and weighed 12 pounds (5,443 Gm) at birth. Labor was difficult and lasted nine hours. Except for pneumonia at the age of 3 months, the child's health had been good. The mother stated that she had had difficulty in keeping the baby clean and dry. The parents and three siblings were in good health. There was no family history of similar deformities.

Physical examination revealed the head, neck, thorax and upper extremities to be normal. The lower extremities presented a peculiar cone-shaped appearance, the thighs being large and flabby and the legs from the knees downward progressively thinner. There was absence of the roundness of the sacrococcygeal region and some shortening of the intergluteal fold (fig 4). As the child was held in a sitting position, there was a soft tissue bulge dorsally at the lumbosacral region. Bilateral talipes equinovarus was noted. As far as could be determined at this age, muscle power and sensation in the lower extremities were unimpaired. There were moderate flexion contractures of the hips and knees.

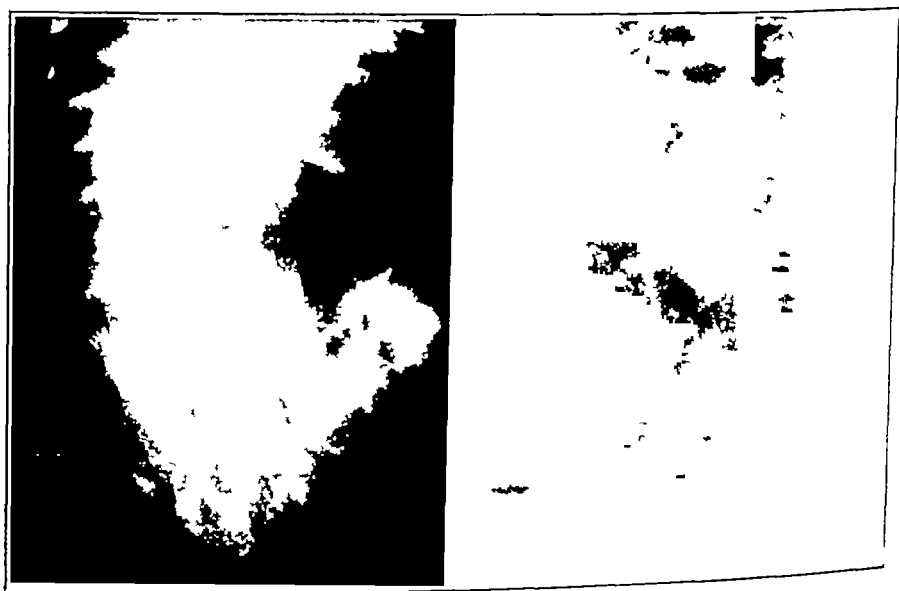


Fig 5 (case 2)—Three lumbar vertebrae and a rudimentary fourth, with spina bifida occulta articulating laterally with the iliac wings. The fifth lumbar vertebra is absent, as are the sacrum and the coccyx. The lateral view shows absence of the fifth lumbar vertebra, the sacrum and the coccyx.

Rectal examination revealed poor sphincter tone. Soft tissue was encountered instead of the bony concavity of the sacrococcyx. Incontinence of urine and feces was noted as the child cried. There were extensive excoriations and numerous pustules over the vulva and buttocks, due to the urine, which seemed to flow almost constantly (fig 4). There was a moderate degree of forward angulation of the pelvis.

Roentgen examination revealed the following abnormalities (fig 5)

- 1 Clubfeet as described
- 2 Three lumbar vertebrae and a rudimentary fourth, with a spina bifida occulta articulating laterally with the iliac wings
- 3 Absence of the fifth lumbar vertebra
- 4 Complete absence of the sacrum and coccyx

Treatment was designed toward correction of the clubfeet in the usual manner. These yielded satisfactorily to corrective casts during a period of three months. The child is now at the hospital for treatment of the contractures of the hip and knee.

A brief resume of cases 3 and 4, previously reported by Hamsa,<sup>1</sup> with a more recent follow-up, is given.

CASE 3—S J, a girl aged 14 months, was born at full term of a 20 year old primipara by normal delivery. Deformities of the spine and legs and shortening of the thighs and torso were noted at birth. There was incontinence of urine and feces. The patient's family history was unimportant. The abnormalities included a short torso, with lumbar kyphosis, dislocation of both hips, clubfeet, flattening of the buttocks, and some atrophy of the thighs. Roentgen examination further revealed spina bifida occulta of the upper part of the dorsal region, partial or complete fusion of the ribs, a right lumbar rib, three rudimentary lumbar vertebrae, and absence of the sacrum and coccyx, with the iliac wings almost touching posteriorly. There was also loss of osseous continuity between the third lumbar vertebra and the pelvis. At the age of 2 years the child could sit alone and could stand by bracing her knees against each other. Operative correction of the feet was advised at that time, but the patient did not return for treatment. A recent follow-up revealed that at the age of 8 years the patient showed little change. She weighed 30 pounds (13.6 Kg), had grown very little and still had no sphincter control. She required a daily enema. She could not walk. No reduction of the dislocated hips was done owing to the malformation of the pelvis.

CASE 4—R S, a 9 year old boy, of normal birth, had four lumbar vertebrae and absence of the sacrum and coccyx, with the iliac wings in close apposition posteriorly. There were congenitally dislocated hips and deformities of the lower extremities. The latter consisted of bilateral ankle valgus and 50 degrees of recurvatum of the left knee, with only a few degrees of flexion from complete extension possible in the right knee. There was atrophy of the thighs and buttocks, with a short intergluteal fold. Urinary and fecal incontinence were complete, but the latter gradually improved. After operative alignment of the lower extremities, the patient could walk with braces and crutches. When he was last seen, two years prior to this report, at the age of 19, there was still considerable weakness of the lower extremities, necessitating crutches. There was good control of the bowels but not of the bladder. Both ankles were in valgus. The patient was getting about however, and was attending business college. No further indication for treatment was made at that time.

#### COMMENT

The characteristic features of partial or complete sacrococcygeal agenesis are well illustrated in the cases presented and resemble closely in their essential features the cases in the literature. Case 1 fits well into group II of Foix and Hillemand's classification, while the other 3 cases are just as typical of group I. The loss of sphincter control is one of the most disturbing features. Spontaneous improvement, especially of the fecal incontinence, occurs, however, as is shown by case 4. Some patients have fecal but not urinary incontinence (Barros Lima<sup>2b</sup>), others have the reverse (de Araujo<sup>3a</sup>).

The case of Diaz Lira <sup>3c</sup> is of interest in that it is the only instance in the literature in which neurolysis of the cauda equina was attempted for the condition. The indication for surgical treatment here, however, followed the development of rectal incontinence and diminution in the deep reflexes of the lower extremities at the age of 3 years. On the basis of these manifestations the cauda equina was explored and scar and fatty tissue were removed from the conglomerate sacral roots, with progressive improvement several days after operation, not only in the rectal incontinence which had recently developed but in the urinary incontinence which had been present since birth. (The patient was a 9 year old boy with conical lower extremities, clubfeet, incontinence of urine and constipation present since birth. There was agenesis of the coccyx and of the last three sacral segments.)

Of interest also is Willemin's <sup>3j</sup> case of a 21 year old man with complete agenesis of the sacral base corresponding to the first sacral segment. The rest of the sacrococcyx was normal. A marked spondylolisthesis of the fifth lumbar vertebra developed. There were no sphincter disturbances, and the lower extremities were normal. This case was the only one of this type of agenesis encountered and does not fit into the classification of Foix and Hillemand <sup>9</sup>. Willemin, however, in his article, stated that he knows of 4 other cases of similar involvement.

The treatment is ordinarily limited to correction of the deformities of the lower extremities by the usual orthopedic measures, as is shown in 3 of the cases reported.

#### SUMMARY

To the 39 cases of partial or complete sacrococcygeal agenesis reported in the literature 2 cases are added, with a review and a recent follow-up study of 2 other cases previously reported from this clinic. The characteristic features and classification of the condition are reviewed. The former include varying degrees of urinary and rectal incontinence, flattening of the buttocks and atrophy and weakness of the lower extremities, with absence of the coccyx and of all or part of the sacrum. Treatment consists of the usual orthopedic measures designed to correct the existing deformities of the lower extremities when enough muscle power is present to enable the patient to assume the erect position.



# FEMORAL HERNIAS

A STUDY OF TWO HUNDRED AND THIRTY-EIGHT HERNIAS  
AND TWO HUNDRED AND TWENTY-SIX REPAIRS

HAROLD J. SHELLEY, M.D.

FORT WORTH, TEXAS

Included in this study were 238 femoral hernias<sup>1</sup>. They comprised 53.5 per cent of the total group of all types of hernias seen in the wards in the period covered by this study. Among these, femoral hernias not previously repaired numbered 222, of which 210 were repaired by operation. Of these, 140 were examined postoperatively for nine months or longer or until a recurrence was discovered. Only 5 recurrences developed, giving a recurrence rate of 3.6 per cent.

The remaining 16 femoral hernias were recurrent, following a previous repair. All 16 were operated on. Thirteen were followed for nine months or longer, and 2 recurrences were discovered, a recurrence rate of 15.4 per cent.

The period covered by this study was from 1916 to 1935 inclusive. All femoral hernias in patients admitted to the wards at St. Luke's Hospital, New York, from 1926 to 1935 and all hernias of this type repaired in the ten year period (1916 to 1925) in patients who returned for follow-up examinations over periods of nine months or longer, or until a recurrence was discovered, were included in this study.

## ETIOLOGIC FACTORS

*Age at Which Hernia Was First Noted*—Primary Hernias. The average age of the patients when these 222 femoral hernias were first noted was 39.6 years.

In the first two decades of life, only 3.2 and 4.1 per cent respectively of these hernias were first noted. This figure was increased to 19.8 per cent for the third decade. The incidence for the fourth, of 25.2 per cent, was the greatest for any decade, although it was only slightly above

From the Surgical Services of St. Luke's Hospital

<sup>1</sup> All references to types of hernias other than femoral are from the following papers published by me: Incomplete Indirect Inguinal Hernias. A Study of 2,462 Hernias and 2,337 Repairs, Arch Surg 41:747-771 (Sept.) 1940, Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs. South. Surgeon 9:257-268 (April) 1940, Direct Inguinal Hernias. A Study of Six Hundred and Five Hernias and Five Hundred and Sixty-Five Repairs, Arch Surg 41:857 (Oct.) 1940, Ventral Hernias. A Study of 550 Hernias and 458 Repairs. South. Surgeon 9:617-656 (Sept.) 1940.

TABLE 1—*Age at Which Hernia Was First Noted*

Age Group, Years	Total Hernias	Per Cent of Entire Group	Number Followed Postopera- tively	Number of Recur- rences	Per Cent Recurrences
0 to 10	7	3.2	3	1	33.3
10 to 20	9	4.1	5	0	0.0
20 to 30	44	19.8	27	1	3.7
30 to 40	56	25.2	36	0	0.0
40 to 50	54	24.3	44	2	4.5
50 to 60	33	14.9	19	1	5.3
60 to 70	11	5.0	5	0	0.0
70 to 80	7	3.2	1	0	0.0
80 to 90	1	0.5	0		
Totals	222	100.0 100.0	140	5	3.6 3.0

The average age at which the femoral hernias were first noted was 39.6 years

TABLE 2—*Age at Time of Admission or Operation (Femoral Hernias)*

Age Group, Years	Total Hernias	Per Cent of Entire Group	Number Followed Postopera- tively	Number of Recur- rences	Per Cent Recurrences
0 to 10	3	1.3	1	0	0.0
10 to 20	7	3.1	6	0	0.0
20 to 30	33	14.8	18	1	5.5
30 to 40	43	19.3	30	1	3.3
40 to 50	64	28.8	46	1	2.1
50 to 60	44	19.8	29	1	3.4
60 to 70	17	7.6	8	1	12.5
70 to 80	9	4.0	2	0	0.0
80 to 90	2	0.9	0		
Totals	222	100.0 100.0	140	5	3.6 3.0

The average age of the patients at the time of admission to the hospital or operation for femoral hernias was 43.7 years

TABLE 3—*Age at Time of Admission or Operation (Recurrent Femoral Hernias)*

Age Group, Years	Total Hernias	Per Cent of Entire Group	Number Followed Postopera- tively	Number of Recur- rences	Per Cent Recurrences
20 to 30	1	6.3	1	0	0.0
30 to 40	3	18.7	3	1	3.3
40 to 50	4	25.0	3	0	0.0
50 to 60	5	31.2	4	1	2.0
60 to 70	2	12.5	1	0	0.0
70 to 80	1	6.3	1	0	0.0
Totals	16	100.0 100.0	13	2	15.4 15.4

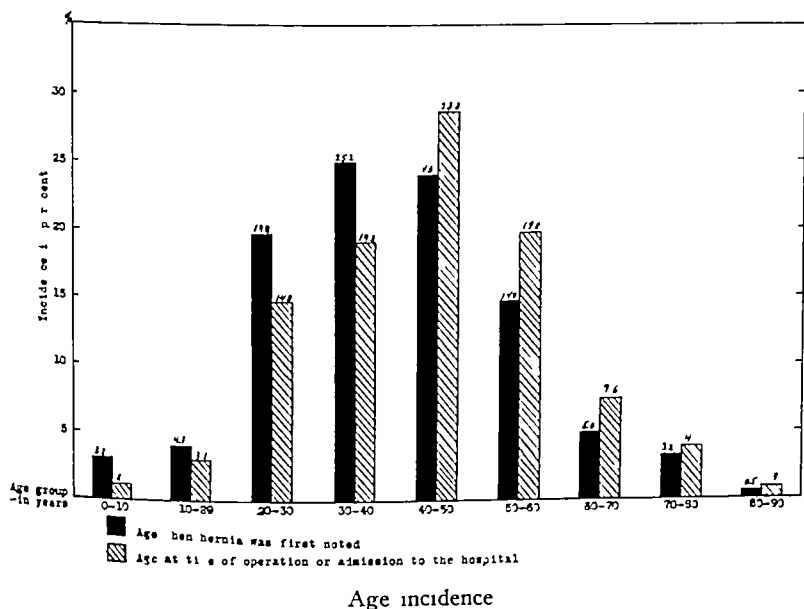
The average age of the patients at the time of admission to the hospital for recurrences of femoral hernias was 49 years

the figure for the fifth decade, 24.3 per cent. The incidence decreased through the succeeding decades to 0.5 per cent for the ninth decade. The incidence for the time covering the child-bearing period of women's lives, from 20 to 50, was 69.3 per cent of all the hernias.

The incidences for the successive twenty year periods of life were 7.3, 4.5, 39.2 and 8.7 per cent respectively.

The number of recurrences was too small for the recurrence rates according to the ages at which the hernias were first noted to have any particular significance.

**Recurrent Hernias.** The average age of the patients when these recurrences were first noted was 41.6 years, 2.1 years less than the



average age at which the primary repairs were done, 43.7 years. Evidently, fewer of the older patients with recurrences came into the hospital for operation. The age of the youngest patient at the time a recurrence was first noted was 22 years, and that of the oldest, 79 years.

The number of repairs was too small for the recurrence rates according to the patients' ages to have any significance.

**Age at Admission or Operation—Primary Hernias.** The average age of the patients with these hernias was 43.7 years.

The age incidences at the time of admission or operation increased from 1.3 per cent for the first decade of life to 28.8 per cent for the fifth. From that period it decreased to 0.9 per cent for the ninth decade. Each decade from the third to the ninth showed 1 recurrence.

The incidences for the successive twenty year periods of life were 4.4, 3.4, 1.4, 48.6 and 12.5 per cent respectively.

TABLE 4—*Sex (Femoral Hernias)*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Male	85	38.3	55	0	0.0
Female	137	61.7	85	5	5.9
Totals	222	100.0	140	5	3.6

TABLE 5—*Sex (Recurrent Femoral Hernias)*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Male	3	18.7	1	0	0.0
Female	13	81.3	12	2	16.7
Totals	16	100.0	13	2	15.4

TABLE 6—*Race (Femoral Hernias)*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
White	217	97.7	138	5	3.6
Negro	5	2.3	2	0	0.0
Totals	222	100.0	140	5	3.6

TABLE 7—*Race (Recurrent Femoral Hernias)*

Race	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
White	16	100.0	13	2	15.4
Negro	0	0.0	—	—	—
Totals	16	100.0	13	2	15.4

TABLE 8—*History of Definite Trauma as Etiologic Factor\**

History of Trauma as Cause*	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
Absent	185	83.3	115	5	4.3
Positive	37	16.7	25	0	0.0
Totals	222	100.0	140	5	3.6

\* Undoubtedly all or a major part of these hernias were present before the onset of the trauma which served only to call the patients' attention to the presence of the hernia. In this connection it is interesting to note that among the 30 complete (congenital) inguinal hernias studied a history of definite trauma as the etiologic factor in the development of their hernias was given by 20 per cent of the patients who first noted the hernia at the age of 15 years (Shelley H. J. Complete Indirect Inguinal Hernias, *Annals of Surgery and Gynecology*, South Surgeon 9: 257-263 (April) 1910).

**Recurrent Hernias** The youngest patient at the time of operation for recurrent femoral hernias was 26 years, the oldest, 79 years. The average age was 49 years. This was the greatest average age at the time of repair for all types of inguinal and femoral hernias. The incidence of the patients' ages at the time of operation increased from the third to the sixth decades of life and then decreased to the eighth.

**Sex—Primary Hernias** Of the 222 primary femoral hernias studied, 61.7 per cent were found in females and 38.3 per cent in males. All of the 5 recurrences were in female patients. None were discovered in the 55 repairs performed on male patients which were observed post-operatively for nine months or longer.

**Recurrent Hernias** The predominance of females among the patients operated on for recurrent femoral hernias, 81.3 per cent, was considerably greater than that found in the case of the original repairs, 61.7 per cent.

**Race—Primary Hernias** Only 5 patients with these hernias were Negroes, 2.3 per cent, 97.7 per cent were white.

**Recurrent Hernias** All 16 patients having recurrent femoral hernias were members of the white race.

**Trauma—Primary Hernias** A history of definite trauma as the etiologic factor in the development of these hernias was given by 16.7 per cent of the patients. (See note under table 8.) That child-bearing may be a definite etiologic factor in their development is indicated by their greatly increased incidence during the years in which women bear children (table 1).

No recurrences were found in the 25 followed patients who had given a history of a definite trauma as the etiologic factor in the development of their hernias.

**Recurrent Hernias** None of the 16 patients with recurrent hernias gave a history of a definite trauma as the cause of the recurrence.

#### SYMPTOMS

**Pain—Primary Hernias** As would be expected with hernias having a small opening into the abdominal cavity, about which is a fairly rigid border, a history of pain associated with their hernias was given by a larger proportion of these patients, 70.7 per cent, than was found to be the case with any type of inguinal hernia.

**Recurrent Hernias** An even greater proportion of patients, 87.5 per cent, with recurrent femoral hernias gave a history of pain associated with the presence of their hernias.

**Duration—Primary Hernias** Somewhat less than half (44.1 per cent) of these hernias were repaired within the first year after they were first noted. The recurrence rate, 1.6 per cent, when they were repaired within the first year was less than half that for the entire group. More

than two thirds, 68 per cent, were repaired within five years, and 82.9 per cent were repaired within ten years, of the time when they were first noted

TABLE 9—*History of Pain Associated with Femoral Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	65	29.3
Positive	157	70.7
Totals	222	100.0

TABLE 10—*History of Pain Associated with Recurrent Femoral Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	2	1.5
Positive	14	87.5
Totals	16	100.0

TABLE 11—*Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
To 1 week	26	11.7	16	0	0.0
To 1 month	39	17.6	21	0	0.0
First 6 months	74	33.3	44	0	0.0
Second 6 months	24	10.8	19	1	5.3
To 1 year	98	44.1	63	1	1.6
0 to 5 years	151	68.0	100	3	3.0
5 to 10 years	33	14.9	23	0	0.0
0 to 10 years	184	82.9	123	3	2.4
10 to 20 years	27	12.2	13	0	0.0
20 to 30 years	9	4.1	3	0	0.0
30 to 40 years	1	0.5	1	0	0.0
40 to 60 years	1	0.5	0	—	—
Totals	222	100.0	140	5	3.6

The average duration (from the time when these hernias were first noted to the time of admission or operation) for femoral hernias was 4.1 years

The average duration (from the time these hernias were first noted to the time of the patient's admission to the hospital) was four and one-tenth years. This was a greater duration than was observed in any type of inguinal hernia with the exception of complete unilateral inguinal hernia.

**Recurrent Hernias** For these hernias the average duration was seven and four-tenths years, the greatest for any type of inguinal or femoral hernias

## PHYSICAL FINDINGS

**Size—Primary Hernias** The sacs of over half (51·8 per cent) of these femoral hernias were not more than  $2\frac{1}{2}$  inches (6·2 cm) in

TABLE 12—Size

Size of Hernia *	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)†	Per Cent Mortality
Size I	115	51·8	70	3	4·3	3 in 74 operations	4·1
Size II	89	40·1	57	2	3·5	3 in 58 operations	5·2
Size III	18	8·1	13	0	0·0	1 in 12 operations	8·3
Totals	222	100·0	140	5	3·6	7 in 144 operations	4·9

\* Size I Hernias in which the greatest diameter of the sac was not more than  $2\frac{1}{2}$  inches (6·2 cm)

Size II Hernias in which the greatest diameter of the sac was more than  $2\frac{1}{2}$  inches and not more than  $3\frac{1}{2}$  inches (8·8 cm)

Size III Hernias in which the greatest diameter of the sac was more than  $3\frac{1}{2}$  inches (8·8 cm)

† All 7 deaths were of patients entering the hospital with strangulated hernias

TABLE 13—Unilateral and Bilateral Hernias \*

	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences
(A)					
Unilateral right	136	61·3	89	3	3·3
Unilateral left	63	28·4	39	2	5·1
Total unilateral	198	89·2	128	5	3·9
Total bilateral	24	10·8	12	0	0·0
Total right	148	66·7	95	3	3·2
Total left	74	33·3	45	2	4·4
Totals	222	100·0	140	5	3·6
(B)					
Bilateral hernias each repaired separately					20
Bilateral hernias both repaired at one sitting					4
No recurrences					

\* Each hernia was counted individually. Each femoral hernia was considered as one of two bilateral hernias when there was or had been a femoral hernia on the opposite side

diameter. Slightly less, 40·1 per cent, had sacs over  $2\frac{1}{2}$  inches and less than  $3\frac{1}{2}$  inches (8·8 cm) in diameter, and only 8·1 per cent had sacs more than  $3\frac{1}{2}$  inches in diameter

The number of recurrences was too small to give definite indications as to the relation of the size of the sac to the probability of recurrence

It is interesting to note that the mortality figure increased with increase in size of these hernias, but the number of hernias in each group was possibly too small for these figures to be conclusive.

**Recurrent Hernias** The groupings of these hernias according to the size of the sac as outlined was 25 per cent, 37.5 per cent and 37.5 per cent respectively, representing a marked decrease in the smallest size and a correspondingly marked increase in the largest.

Among the repairs of the smaller hernias were no operative deaths or recurrences. After repairs of the largest hernias, the mortality rate was 25 per cent and the recurrence rate 20 per cent.

**Unilateral and Bilateral Hernias—Primary Hernias** The incidence of bilateral femoral hernias, 10.8 per cent, was only one third that of incomplete indirect inguinal hernias, 32.6 per cent. The incidence of

TABLE 14—*Incarceration and Strangulation (Femoral Hernias)*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	102	45.9	68	3	4.5	0 in 52 operations	0.0
Incarcerated *	94	42.4	59	2	3.4	3 in 74 operations*	4.1
Strangulated *	37	16.7	20	0	0.0	7 in 27 operations*	25.9
Totals	222	100.0	140	5	3.6	7 in 144 operations*	4.9

\* Strangulation developed in 11 of 102 incarcerated hernias. Strangulation was present in all 7 patients who died postoperatively. In 3 of these the hernia had been incarcerated previous to the development of the strangulation.

femoral hernias on the right side, 66.7 per cent, was greater than the incidence of incomplete indirect inguinal hernias on the right side, 55 per cent.

The probability of recurrence following repair contrasting unilateral with bilateral and right with left femoral hernias cannot be given from this study, as not a sufficiently large number were studied in each group for the recurrence figures to have any significance.

**Recurrent Hernias** In 12.5 per cent of the patients with recurrent femoral hernias there was a femoral hernia on the opposite side at the same time, or there had previously been one. This is essentially the same as the incidence of bilateral primary femoral hernias, 10.8 per cent.

In such a small number of repairs, the recurrence rates cannot be taken as significant as to the probability of recurrence when the hernias are unilateral or bilateral.

**Incarceration and Strangulation—Primary Hernias** The incidence of incarceration and strangulation were considerably increased in femoral hernias as compared to incomplete indirect inguinal hernias. This is the natural expectation because of the small opening in the



abdominal cavity with a relatively rigid circumference. Of the 222 femoral hernias, 42.4 per cent were incarcerated, as contrasted to only 6 per cent in the incomplete indirect inguinal hernias. The figures were 16.7 per cent and 1.8 per cent respectively for strangulation.

So far as the respective incidence rates of the small number of recurrences would indicate, incarceration and strangulation bore no relation to the probability of recurrence following repairs of femoral hernias.

However, these two conditions had a direct bearing on the mortality following operative repair. In the presence of incarceration of femoral hernias the mortality rate was 4.1 per cent, but all the deaths making up this figure were associated with incarcerated hernias which had later become strangulated. For strangulated femoral hernias the mortality rate in 27 operations was 25.9 per cent. There were no deaths associated with the 52 operations on femoral hernias which were neither

TABLE 15—*Incarceration and Strangulation (Recurrent Femoral Hernias)*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	5	31.2	5	1	20.0	0 in 5 operations	0.0
Incarcerated *	10	62.5	8	1	12.5	1 in 10 operations†	10.0
Strangulated *	3	18.7	1	0	0.0	1 in 3 operations†	33.3
Totals	16	100.0	13	2	15.4	1 in 16 operations†	6.3

\* Strangulation developed in 2 old incarcerated hernias

† The patient who died had strangulation in an old incarcerated hernia

incarcerated nor strangulated. (Mortality rates were calculated only on the repairs performed between 1926 and 1935.)

**Recurrent Hernias.** Larger percentages of these hernias were incarcerated, 62.5 per cent, and strangulated, 18.7 per cent, than was the case with femoral hernias which were not recurrent, 42.4 and 16.7 per cent respectively.

The relation of incarceration and strangulation to the incidence of recurrence and mortality was essentially the same as with the original femoral repairs, with the exception of an increased percentage in each instance. The only patient who died after operation had a strangulated hernia, but this hernia was incarcerated before the development of strangulation.

#### RESULTS ACCORDING TO TYPE OF OPERATIONS

**Primary Hernias.**—The variations in the technic of repairing these hernias were considered too slight to warrant tabulating the figures as to results according to the different types of repair. The number of recurrences was so small that the figures would have had no value in deter-

mining the comparative success of these operations All hernias were repaired from below Poupart's ligament This structure was sutured to the pectineus fascia with ordinary sutures, mattress sutures or, in a few instances, a purse string suture Silk was used in only a few repairs

*Recurrent Hernias*—All but 1 of these recurrent hernias were repaired with catgut suture material alone The recurrence rate for these repairs was 167 per cent, and in 20 per cent of these operative wounds infection developed

TABLE 16—*Postoperative Respiratory Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Number Post-operative Stay in Hospital, Days	Number of Post-operative Operations	Number of Recurrences	Per Cent of Recurrences	Per Cent of Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	6	2.9	16.5	3	0	0.0	0.0	0	0.0
2 Lobar pneumonia	2	0.9	16.0	1	0	0.0	0.0	1	50.0
3 Bronchopneumonia	1	0.48	4.0	0	0	0.0	50.0	1	100.0
4 Acute tonsillitis	1	0.48	15.0	1	0	0.0	0.0	0	0.0
Totals	10	4.8		5	0	0.0	10.0	2	20.0

TABLE 17—*Postoperative Circulatory Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Number Post-operative Stay in Hospital, Days	Number of Post-operative Operations	Number of Recurrences	Per Cent of Recurrences	Per Cent of Infected Wounds	Deaths	Per Cent Mortality
1 Hematomas	3	1.4	14.6	3	0	0.0	0.0	0	0.0
2 Deep phlebitis	3	1.4	24.0	3	0	0.0	0.0	0	0.0
Totals	6	2.8		6	0	0.0	0.0	0	0.0

Only one repair was performed with a fascial suture from the fascia lata This wound healed without infection, and no recurrence had developed when the patient was last examined, two years after the operation

#### POSTOPERATIVE COMPLICATIONS

*Primary Hernias*—The incidence of postoperative complications was 50 per cent greater after repair of femoral hernias (15.6 per cent) than after repair of incomplete indirect inguinal hernias (10.4 per cent) The reason for this was not apparent The major complications appeared in much the same order, but deep phlebitis, which followed only 0.3 per cent of the inguinal repairs, was found after 1.4 per cent of the femoral repairs

The incidence of respiratory complications, 4.8 per cent, was slightly more than half that found after repairs of incomplete indirect inguinal hernias, 7.3 per cent

TABLE 18—Miscellaneous Postoperative Complications

Complication	Total Operations	Per Cent of Entire Group	Average Number Post operative Stay in Hospital Days	Number of Recurrences	Per Cent of Recurrences	Per Cent of Infected Wounds	Per Cent of Deaths	Per Cent Mortality
1 Wound infection	11	5.2	17.8	8	0.0		0	0.0
2 Acute bronchitis	0	2.9	16.5	3	0.0	0.0	0	0.0
3 Hematomas	3	1.4	14.6	3	0.0	0.0	0	0.0
4 Deep phlebitis	3	1.4	24.0	3	0.0	0.0	0	0.0
5 Lobar pneumonia	2	0.9	16.0	1	0.0	50.0	1	50.0
6 Bronchopneumonia	1	0.48	4.0	0		0.0	1	100.0
7 Acute tonsillitis	1	0.48	15.0	1	0.0	0.0	0	0.0
8 Cystitis	1	0.48	19.0	1	0.0	0.0	0	0.0
9 Pyelitis	1	0.48	60.0	0		0.0	0	0.0
10 Acute appendicitis	1	0.48	21.0	1	0.0	0.0	0	0.0
11 Acute cholecystitis	1	0.48	29.0	1	0.0	0.0	0	0.0
12 Paralytic ileus *	1	0.48	1.0	0		0.0	1	100.0
13 Bacillus welchii peritonitis *	1	0.48	2.5	0		100.0	1	100.0
Totals	33	15.6		22	0.0	6.1	4†	12.1

\* These complications both developed in patients who had had strangulated hernias

† Three patients died as a result of the toxemia from the preoperative intestinal obstruction

TABLE 19—Deaths (Femoral Hernias, 1926-1935)

Operative Deaths *	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death (Post operative)	Cause of Death
1	44	Yes	18 hours	No †	2½ days	B. welchii wound infection and peritonitis
2	52	Yes	1 week	No	Immediately	Toxemia from long standing strangulation and shock
3	69	Yes	3 days	No	3 days	Lobar pneumonia coronary fibrosis myocardial sclerosis pyelonephritis
4	69	Yes	3 days	No	4 days	Bronchopneumonia arteriosclerotic heart disease
5	70	Yes	4 days	No	12 hours	Toxemia from long standing strangulation shock
6	87	Yes	6 days	Yes	24 hours	Paralytic ileus
7	68	Yes	4 days	†	10 hours	Toxemia intestinal obstruction

\* Seven deaths in 144 operations, giving an operative mortality of 4.9 per cent

† Small area of gangrene in a Richter type hernia. The area of gangrene was inverted

‡ Enterostomy in the strangulated loop. No repair of the hernia was done

TABLE 20—Deaths (Recurrent Femoral Hernias 1926-1935)

Operative Deaths *	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death	Cause of Death
1	70	Yes	6 hours	No	2 hours after operation	Ileus shock

One death in 16 operations giving an operative mortality of 6.3 per cent

The incidences of circulatory complications were the same following repairs of femoral and of incomplete indirect inguinal hernias, 2.8 per cent

*Recurrent Hernias*—The incidence of postoperative complications was greater after repair of recurrences than after the original operations. Complications developed after 18.8 per cent of these operations, as compared to 15.6 per cent of original femoral repairs. Respiratory complications followed 6.3 per cent of the repairs of recurrences, as compared with 4.8 per cent, and circulatory complications after 6.3 per cent as compared with 2.8 per cent

#### OPERATIVE MORTALITY

*Primary Hernias*—The operative mortality of 4.9 per cent (as compared to 0.52 per cent in incomplete indirect inguinal hernias) was due

TABLE 21—*Follow-Up Data (Femoral Hernias)*

Total number of hernias studied	222
Total with no operation	12
Total operations	210
Deaths (all operative)	7
Total with no follow up examination	34
Total with follow up under 9 months (no recurrences)	20
Total with follow up 9 months and over (including recurrences)	140
Average follow up time (all cases followed 9 months and over)	24.9 months
Total recurrences	0
Average postoperative time recurrences were first noted	26.8 months
Percentage of recurrences (follow up 9 months and over)	3.6
Total number of operations examined postoperatively	170
Average follow up time (all followed cases)	21.7 months
Total recurrences	0
Percentage of recurrences (all followed cases)	2.9

to 7 deaths, all following repairs of strangulated hernias. The various facts about these 7 deaths are given in table 19.

*Recurrent Hernias*—One death followed repair of 16 recurrent femoral hernias, a mortality rate of 6.3 per cent. The patient, who was 79 years of age, had had a strangulation for six hours. She died two hours after the operation, of ileus, shock and preoperative toxemia and dehydration. No resection was required.

#### FOLLOW-UP DATA

*Primary Hernias*—Of the 222 femoral hernias studied, 12 were not repaired. There were 7 operative deaths, and 34 patients did not return for follow-up examination. One hundred and forty were followed for nine months or longer, for an average period of twenty-four and nine tenths months. Only 5 recurrences were discovered, an incidence of 3.6 per cent. The average postoperative time at which the recurrences were first noted was twenty-six and eight-tenths months.

A total of 170 were examined in the follow-up clinic. The average follow-up time for all followed repairs was twenty-one and two-tenths months. The recurrence rate calculated on all follow-up examinations was 2.9 per cent.

*Recurrent Hernias*—All of the 16 patients with recurrent femoral hernias were operated on. One died postoperatively. Thirteen of the remaining 15 were followed for nine months or longer. The average follow-up period was thirty-three and two-tenths months. Two recurrences were discovered, giving a recurrence rate of 15.4 per cent. The average postoperative time at which these recurrences were discovered was ten months.

Fourteen patients altogether were examined in the follow-up clinic. The average follow-up time was thirty and one-tenth months and the recurrence rate 14.3 per cent.

TABLE 22—*Follow-Up Data (Recurrent Femoral Hernias)*

Total number of hernias studied	16
Total with no operation	0
Total operations	16
Total operative deaths	1
Total with no follow up examination	1
Total with follow up under 9 months (no recurrences)	1
Total with follow up 9 months and over (including recurrences)	13
Average follow up time (all cases followed 9 months and over)	32.2 months
Total recurrences	2
Average postoperative time when recurrences were first noted	10.0 months
Percentage of recurrences (follow up 9 months and over)	15.4
Total number of operations examined postoperatively	14
Average follow up time (all followed cases)	30.1 months
Total recurrences	2
Percentage of recurrences (all followed cases)	14.3

#### REPAIR OF FEMORAL HERNIAS

*Primary Hernias*—It is probably unnecessary to go into great detail as to the technic of repair of femoral hernias. With careful, intelligent surgical handling, satisfactory results will ensue whatever the method of repair.

The question of the type of incision in the skin and subcutaneous tissues is largely that of the individual preference of the surgeon. In the presence of an inguinal hernia associated with a femoral hernia, naturally an oblique incision should be used. In those few instances in which there is a possibility that the hernia may be inguinal instead of femoral, again the oblique incision should be used.

The necessity of an approach to the neck of the sac from above the inguinal ligament will present in few repairs if the surgeon is familiar with the anatomy of the femoral region and the technic of carrying out the various necessary procedures in that region.

Careful, clean dissection of the structures about the femoral ring is an important point. Location of the interior of the sac without injury to its contents at times will present certain difficulties. This is due to (1) adherence of the contained omentum or intestine to the peritoneal lining of the sac, (2) cystic degeneration of the incarcerated omentum, giving false pockets simulating the interior of the sac, and (3) edema or even cystic degeneration of the fat and other tissues making up the hernial sac itself. This difficulty can usually be avoided by opening the sac near the neck, where these various conditions do not ordinarily present themselves.

When the femoral canal is too small for reduction of the contents of the sac into the abdomen, incision of Gimbernat's ligament will ordinarily suffice to permit the contents to be returned to the abdomen. An occasional rare case will be observed in which additional careful enlargement of the femoral ring by retraction laterally will be necessary.

I believe that when a resection is necessary it should be done through a lower rectus incision. Reduction of the anastomosed loops of intestine through the femoral opening may damage the anastomosis, and the resection itself may well contaminate the operative wound and thereby greatly increase the probability of recurrence of the hernia.

In my experience, reduction of the strangulated loop for a time into the abdominal cavity has frequently demonstrated that a resection was unnecessary, while observation of that same strangulated loop in the operative wound, even though the femoral opening had been apparently adequately enlarged, would indicate that resection was required.

Avoidance of unnecessary resections will reduce markedly the operative mortality associated with strangulated femoral hernias.

As to closure of the femoral canal itself, any of the various technics, if properly applied, will give satisfactory results. My preference in this respect is for mattress sutures reenforced by two or three ordinary sutures. The lateral suture should be applied with the femoral vein carefully retracted laterally. In closure of the wound, all dead spaces should be carefully eliminated. Use of silk throughout for suture and ligature material is a distinct improvement over use of catgut.

With the exception of those cases in which there is an unusually large femoral opening and those in which this opening has been markedly enlarged in order to reduce the contents of the sac, these patients do not require as long a period of time in bed postoperatively as should be insisted on after repairs of inguinal hernias. However, it is even more important that these patients have their position in bed changed frequently immediately after the operation and that active movements be instituted as early as possible and kept up until the patients are permitted out of bed. In this series of repairs the incidence of deep phlebitis was four times that which followed repair of incomplete indirect inguinal hernias.

*Recurrent Hernias*—Repair of the majority of recurrent femoral hernias will not differ materially from repair of primary hernias except that dissection of the sac and the various anatomic structures will present added difficulties due to the scar of the previous operation. In most cases a careful repair, preferably with mattress sutures, will give satisfactory closure of the defect.

When part of the inguinal ligament has been lost in the failure of the original repair, reconstruction of this structure and closure of the large femoral canal with a suture or sutures obtained from the fascia lata will be required in order to obtain a satisfactory result.

The use of silk for sutures and ligatures in every case is a worthwhile addition to the technic, particularly since these wounds are prone to fill up with serum when catgut is used.

Patients in whom a recurrent femoral hernia has been repaired should be kept in bed longer than in the case of the primary repairs. The additional time is to be determined by the nature of the repair required in each individual case.

1213 Medical Arts Building

# PARENTERAL ADMINISTRATION OF A WATER-SOLUBLE COMPOUND WITH VITAMIN K ACTIVITY

4 AMINO 2 METHYL 1 NAPHTHOL HYDROCHLORIDE

EDWARD R ANDERSON, MD

JOHN E KARABIN, MD

HERBERT UDESKY, MD

AND

LINDON SEED, MD

CHICAGO

A water-soluble compound with vitamin K activity, 4-amino-2-methyl-1-naphthol hydrochloride, has been synthesized by Doisy and his associates<sup>1</sup> The oil-soluble vitamin K, 2-methyl-1,4-naphthoquinone, has been found very active when administered orally,<sup>2</sup> but since it is relatively insoluble in water, it is inconvenient for parenteral use Parenteral administration of vitamin K has several advantages over oral administration By the oral route, there may be a lack of absorption due to intestinal obstruction, paralytic ileus or some other intestinal complication By the parenteral route the vitamin may be given to patients who are unable to take it orally because of nausea or vomiting In the treatment of hemorrhagic disease of the newborn, for which vitamin K is very effective, the parenteral method is especially indicated When the substance is administered parenterally it is not necessary to give bile salts With oral administration bile salts must be present in order to assure absorption of the vitamin

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From the Department of Surgery of the University of Illinois College of Medicine and the Cook County Hospital

1 Doisy, E A , MacCorquodale, D W , Thayer, S A , Binkley, S A , and McKee, R W The Isolation, Constitution and Synthesis of Vitamin K, *Science* **90** 407, 1939 Thayer, S A , Binkley, S A , MacCorquodale, D W , Doisy, E A , Emmett, A D , Brown, R A , and Bird, O D Vitamin K Potencies of Synthetic Compounds, *J Am Chem Soc* **61** 2563, 1939

2 (a) Anderson, E R , Karabin, J E , Udesky, H , and Seed, L The Oral Administration of Synthetic Vitamin K, to be published (b) Rhoads, J E and Fliegelman, M T The Use of 2-Methyl-1,4-Naphthoquinone (a Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency, *J A M A* **114** 400 (Feb 3) 1940 (c) Macfie, J M , Bacharach, A L , and Charce, M R A Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, *Brit. M J* **2** 1220, 1939



Before the synthesis of the water-soluble compound, phthiocol had been found to contain vitamin K activity (Almquist and Klose<sup>3</sup>) and had been used intravenously. Phthiocol was isolated by Anderson and Newman<sup>4</sup> from the pigment of the tubercle bacillus and was found to be 3-hydroxy-1,4-naphthoquinone. Smith<sup>5</sup> and also Butt, Snell and Osterberg<sup>6</sup> reported good results after using phthiocol intravenously. Ansbacher and Fernholz<sup>7</sup> found the potency of this compound to be about one hundred times less than that of vitamin K concentrates. However, the oil-soluble 2-methyl-1,4-naphthoquinone was almost as active as the vitamin K concentrates in pure form. Thus, phthiocol was not a satisfactory parenteral substitute for vitamin K. Rhoads and Fliegelman<sup>2b</sup> used 2-methyl-1,4-naphthoquinone, 1 mg in 10 cc of physiologic solution of sodium chloride, intravenously in 1 case, with a good response, but its relative insolubility made it inconvenient for general use. Sharp and his associates<sup>8</sup> found that 4-amino-2-methyl-1-naphthol hydrochloride contains vitamin K activity. Infants and patients with obstructive jaundice,<sup>9</sup> as well as experimental animals, responded satisfactorily within twelve hours<sup>10</sup>.

The soluble synthetic compound used in this investigation was 4-amino-2-methyl-1-naphthol hydrochloride,<sup>11</sup> for convenience in this report it will be designated as vitamin K<sub>s</sub>. The prothrombin determinations were done by the Smith method. The value for plasma prothrombin is reported as the per cent of prothrombin clotting activity and represents the per cent of normal.

3 Almquist, H. J., and Klose, H. H. The Antihemorrhagic Activity of Certain Naphthoquinones, *J Am Chem Soc* **61** 1923, 1939.

4 Anderson, R. J., and Newman, M. S. The Chemistry of the Lipids of Tubercle Bacilli, *J Biol Chem* **101** 773, 1933.

5 Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R. Clinical and Experimental Studies on Vitamin K, *J A M A* **113** 380 (July 29) 1939.

6 Butt, H. R., Snell, A. M., and Osterberg, A. E. Phthiocol Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice, a Preliminary Report, *Proc. Staff Meet., Mayo Clin* **14** 497, 1939.

7 Ansbacher, S., and Fernholz, E. Simple Compounds with Vitamin K Activity, *J Am Chem Soc* **61** 1924, 1939.

8 Sharp, E. A., Emmett, A. D., and Kamm, O. The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Naphthol, *J Biol Chem* **133** 285, 1940.

9 Sharp, E. A., Vonder Heide, E. C., and Good, W. H. Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, to be published.

10 The work was done in the research laboratory of Parke, Davis & Company.

11 The material used in the clinical experiments herein reported was furnished by Parke, Davis & Company, who have called it vitamin K<sub>s</sub>. Each ampule contains 1 mg of the substance dissolved in 1.4 cc of water.

Eighteen patients were given this compound parenterally to study its therapeutic effect, it was hoped thereby to compare its efficiency with that of the insoluble vitamin K previously used. Seventeen patients responded favorably, while 1 did not. The patient last mentioned had fatal acute yellow atrophy of the liver due to antisyphilitic therapy. Apparently the entire liver had been destroyed, this destruction producing a condition comparable to that observed after complete hepatectomy. Since the liver is necessary for the manufacture of pro-

TABLE 1—*Jaundiced Patients Who Received Vitamin K<sub>3</sub>*

Patient	Diagnosis	Jaundice		Prothrombin Activity	After Vitamin K
		Duration	Degree		
A N	Acute yellow atrophy of liver	2 weeks	4	37%	37%
A R	Metastatic carcinoma	6 weeks	4	50%	100%
O H	Carcinoma of ampulla of Vater	2 months	4	67%	100%
S V	Carcinoma of pancreas	2 months	4	70%	100%
C P	Carcinoma of pancreas	1 month	3	61%	90%
M C	Carcinoma of pancreas	2 months	3	64%	94%
S D	Carcinoma of pancreas	3 weeks	3	65%	100%
J W	Carcinoma of pancreas	3 weeks	2	65%	100%
A W	Acute cholecystitis	2 weeks	2	75%	100%
O M	Cholelithiasis	2 weeks	1	62%	100%
W O	Catarrhal jaundice	2 days	1	55%	98%
J L	Toxic hepatitis	12 days	1	50%	95%
H M	Cholelithiasis	10 days	1	64%	94%
A M	Cholelithiasis	1 month	1	61%	100%

Grade 1, slight, 2, moderate, 3, severe, 4, very severe

TABLE 2—*Nonjaundiced Patients Who Received Vitamin K<sub>3</sub>*

Patient	Diagnosis	Prothrombin Activity	After Vitamin K
J S	Cholelithiasis	80%	100%
A K	Empyema of gallbladder	67%	100%
J W	Cirrhosis of liver	67%	100%
C A	Carcinoma of rectum	69%	85%

thrombin through vitamin K, this negative result was to have been expected. Of the 18 patients, 13 (table 1) had hypoprothrombinemia due to jaundice, and 5 (table 2) had hypoprothrombinemia due to other conditions. No patients had any signs of bleeding, for the hypoprothrombinemia was not allowed to reach dangerous levels.

The average initial dose was 2 to 3 mg given intravenously and followed by 3 mg daily as a maintenance dose. Some patients received 1 mg daily and responded favorably, while others needed larger doses. The intramuscular dosage used was the same. However, this method of administration was not as satisfactory as the intravenous route. The case of O M (chart 1), a patient with cholelithiasis and jaundice due to secondary hepatitis, illustrates the intravenous therapy followed

The level of plasma prothrombin before operation was 84 per cent. On the first day following cholecystectomy the level dropped to 62 per cent. Two milligrams of vitamin K<sub>5</sub> was given intravenously, and in one-half hour the level reached 86 per cent. In two hours it was 100 per cent. Twenty-four hours later it had dropped to 71 per cent. At this time 1 mg was given intravenously three times a day. The prothrombin level returned to normal and remained there with this regimen. H. M. (chart 2), a patient with jaundice due to a common stone, illustrated the more gradual response by the intramuscular

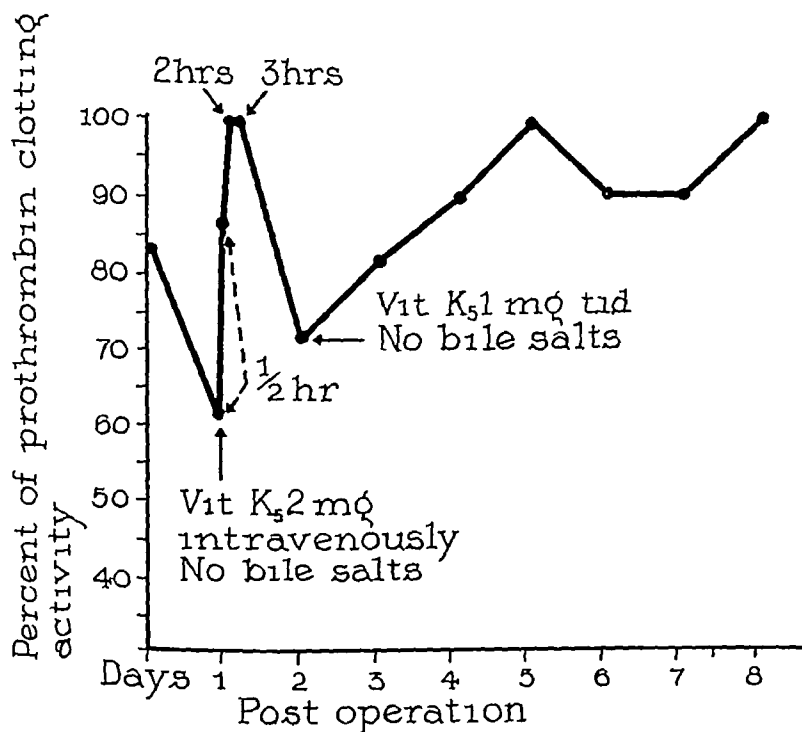


Chart 1—Record in the case of O. M., a patient with cholelithiasis with jaundice. Note the sharp return of prothrombin clotting activity to normal within two hours after intravenous administration of 2 mg of vitamin K<sub>5</sub> on the first postoperative day. A day later the prothrombin activity had dropped to 71 per cent.

A daily dose of 1 mg three times per day brought the level back to normal where it was maintained. The patient had jaundice—presumably secondary to hepatitis, since there was no stone in the common duct.

route. The prothrombin level on the first day following a choledochostomy was 83 per cent, on the second, 70 per cent, and on the third, 64 per cent. Three milligrams of vitamin K<sub>5</sub> was given intramuscularly. In one hour the level was 75 per cent, in two hours 76 per cent, and in three hours, 80 per cent. The per cent then dropped to

74 in four hours. Three milligrams of vitamin  $K_2$  was given intramuscularly with 1 Gm of bile salts by mouth. In one hour the level increased to 78 per cent, in two hours, to 84 per cent, and in three hours, to 86 per cent. The level again dropped in twenty-four hours to 67 per cent. Vitamin  $K_2$  (2-methyl-1,4-naphthoquinone), 24 mg with 1 Gm of bile salts, was given by mouth. In twenty-four hours the level was 88 per cent, in forty-eight hours, 90 per cent, and in seventy-two hours, 96 per cent. This level was maintained. However, the patient was improving generally, and the two factors were probably responsible for the continued oral improvement.

The response to the intravenously given vitamin K-active compound occurred within three-quarters of an hour to one and one-half

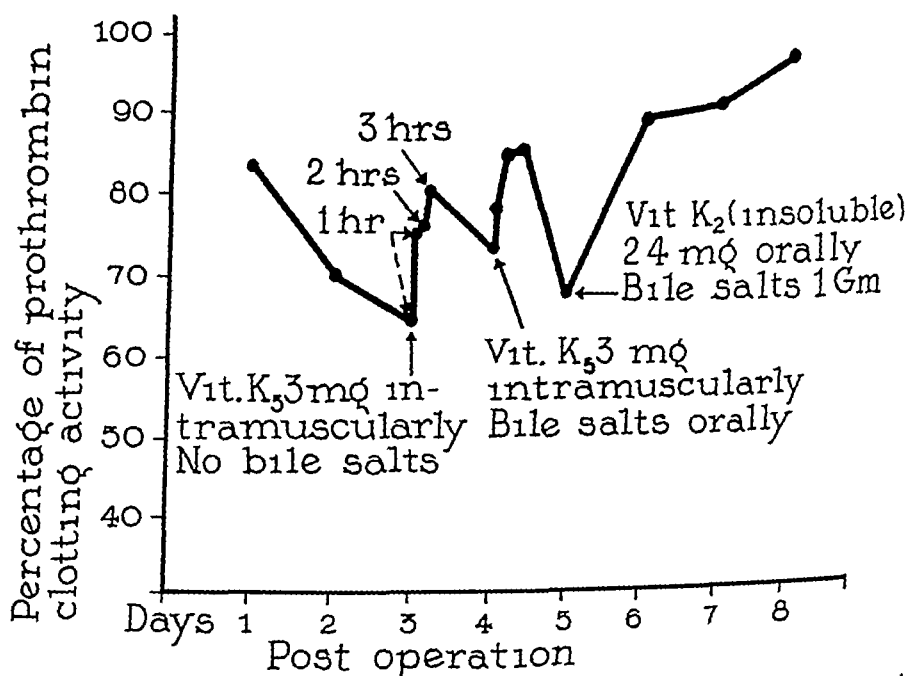


Chart 2—Record in the case of H. M., a patient with choledocholithiasis and jaundice. Choledochostomy was performed. Note the drop in prothrombin clotting activity after operation, with a gradual response to intramuscular injection of 3 mg of vitamin  $K_2$ . No difference in response to the vitamin  $K_2$  is noted with the administration of bile salts orally.

Oral administration of vitamin  $K_2$  maintained the level within normal limits

hours. Patients with relatively good hepatic function showed normal levels of plasma prothrombin within two hours after the administration of the active compound. However, patients with damaged livers often did not reach a normal level of plasma prothrombin until twelve hours had elapsed, others never reached normal levels, in spite of the prolonged therapy. As has been stated, A. N., a patient with a severe degree of jaundice due to acute yellow atrophy of the liver, did not respond to 6 mg of the active compound given intravenously. The

indicates the importance of the liver in the formation of the plasma prothrombin. Thus, clinically the patients with severe damage to the liver did not give as good a response to the compound or maintain the level of plasma prothrombin as well as those with relatively good hepatic function. In one-half hour, O M (chart 1) showed a rapid response to 2 mg given intravenously. The plasma prothrombin activity rose 24 per cent in one-half hour and 38 per cent in two hours. Other patients did not respond so quickly. In the case of C K the value rose 20 per cent in three quarters of an hour, in the case of C A, 16 per cent in one hour, in the case of M C, 28 per cent in one hour, and in the case of A W, 15 per cent in one and one-half hours.

The dose of the vitamin K-active compound needed to maintain the plasma prothrombin varied with the individual patient. Maintenance doses could be estimated only by repeated prothrombin determinations. One milligram three times a day or 3 mg in one dose was a satisfactory amount for maintenance (case of O M, chart 1). After an initial dose of 3 mg the concentration of plasma prothrombin rose to normal, but it frequently dropped again on the following day. We thought that the effect of this water-soluble vitamin K compound was as good as that of the oil-soluble active compound. Broun<sup>12</sup> used an initial 5 mg dose of the vitamin K<sub>3</sub> in 1 instance and obtained a good response which extended over several days.

No bile salts were necessary for a response to vitamin K<sub>3</sub> given parenterally. No toxic manifestations were observed. As much as 6 mg at one dose was given intravenously without harm to the patient. Several patients were given 0.33 Gm (a 5 grain capsule) of bile salts orally for each milligram of vitamin K<sub>3</sub> given intravenously. No difference in the response or in the maintenance requirement was observed. Therefore, bile salts need not be given when parenteral vitamin K therapy is used. However, the value of bile salts for patients who are not secreting bile salts into the intestinal tract must be recognized. The deficiency of bile salts may produce adverse effects in the body economy not related to prothrombin.

Intravenous administration of the synthetic soluble active compound has an advantage over administration by the intramuscular route. The response is quicker, and the effect is greater. Chart 1 illustrates results of using the intravenous route. The response was quick, and a normal level of prothrombin was reached within two hours. Chart 2 illustrates a gradual and incomplete response to intramuscular therapy. From our observations the potency of 4-amino-2-methyl-1-naphthol hydrochloride, the water-soluble synthetic compound seems equal in effect

12 Broun, G O, in discussion on Sharp, E A. Vitamin K Activity of 2 Methyl 4-Naphthoquinone. J A M A 114 439 (Feb 3) 1940

to the oil-soluble synthetic compound. The advantage of vitamin  $K_3$  over the water-insoluble vitamin K compound therefore lies in the fact that it can be given at any time, even though the patient may be vomiting and unable to retain or absorb drugs given orally.

We were unable to obtain an appreciable elevation of the level of plasma prothrombin above normal with the parenteral active compound. In several instances a 5 per cent increase above the normal level of plasma prothrombin was observed.

#### SUMMARY

A water-soluble synthetic compound with vitamin K activity for parenteral use was effective in 17 of 18 patients with hypoprothrombinemia. The patient who failed to show a response had acute yellow atrophy of the liver.

Intravenous administration is superior to intramuscular. The ease of administration should determine whether the drug is to be given orally or intravenously.

The intravenous dose is approximately 2 to 3 mg daily. The response occurs within three quarters of an hour to one and one-half hours after administration. Patients with relatively good hepatic function showed normal plasma prothrombin levels within two hours, while patients with damaged livers reached normal levels in twelve hours or did not reach normal levels in spite of prolonged vitamin  $K_3$  therapy.

Clinically, patients with severe damage of the liver did not give as good a response to the vitamin K-active compound or maintain the level of plasma prothrombin as well as patients with relatively good function of the liver.

The maintenance dose of the vitamin K-active compound varies with the individual patient and can be found only by repeated prothrombin determinations. No toxic effects were observed following doses up to 6 mg.

Bile salts are not necessary for the action of the drug when it is given either intravenously or intramuscularly.

The effect of vitamin  $K_3$  is no greater than that noted after the use of the water-insoluble vitamin K compound, but vitamin  $K_3$  has the distinct advantage that it can be given at any time in the preoperative or postoperative course, regardless of whether the patient is able to take and absorb drugs by mouth.

# ROLE OF INTRALUMINAL OBSTRUCTION IN THE PATHOGENESIS OF ACUTE APPENDICITIS

HARRY KOSTER, M D  
AND  
ARTHUR SHAPIRO, M D  
BROOKLYN

In the past few years several papers<sup>1</sup> on acute appendicitis have stressed the role of increased intraluminal pressure as a factor in the development of the lesion. Since the maximum intraluminal pressure can never exceed the pressure at which the appendix will empty into the cecum, studies were undertaken on the initial resistance to perfusion of unselected normal and diseased appendixes both in situ and after excision.

## METHOD

Eighteen appendixes were studied in situ. After the appendix was delivered into the wound it was held by an Allis clamp applied to the mesentery as it joined the tip, and a transfusion cannula was passed into the lumen of the organ through the tip. The cannula was then connected to an easily controlled pressure system (water) with a glass tube side arm in which the fluid level could be observed. The pressure was slowly raised, and the height at which the level could no longer be sustained was considered the maximal initial perfusion resistance pressure. Appendectomy was then performed.

Twenty-five appendixes were studied after being removed without clamping or handling. The mesoappendix was picked up with an Allis clamp, and the appendix was delivered into the wound. The mesoappendix was tied and cut. Another ligature was tied around the cecum about 1 cm from the base of the appendix. A purse-string suture was placed in the cecum. The appendix was excised with that portion of the cecum beyond the ligature, and the stump was inverted by the purse-string suture. The tip of the appendix was then cut off, and a cannula

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From the Crown Heights Hospital

1 (a) Wangensteen, O H, and Dennis C. *Ann Surg* **110** 629, 1939. (b) Bowers, W F. *Appendicitis, with Especial Reference to Pathogenesis, Bacteriology and Healing*, *Arch Surg* **39** 362 (Sept) 1939. (c) Dennis, C, Buirge, R E, and Wangensteen, O H. *Surgery* **7** 372 1940. (d) Wangensteen, O H. *Proc Inst. Med. Chicago* **12** 266, 1939. (e) Wangensteen, O H, Buirge, R E, Dennis C, and Ritchie, W P. *Ann Surg* **106** 910 1937. (f) Wangensteen, O H, and Bowers, W F. *Significance of Obstructive Factor in Genesis of Acute Appendicitis. Experimental Study*, *Arch Surg* **34** 496 (March) 1937.

was tied a few millimeters into the lumen. The initial resistance to perfusion was then determined in the same way as in the unexcised specimens. All specimens were then examined histologically.

TABLE 1—*Initial Resistance to Perfusion of Unexcised Appendixes*

Case	Perfusion Resistance Pressure, Cm	Fecolith	Condition of Organ	Operation	Comment
1	Over 150	+	Acute gangrenous appendicitis	Appendectomy	
2	Over 150	+	Acute suppurative appendicitis	Appendectomy	
3	Over 150	+	Acute suppurative appendicitis	Appendectomy	
4	134	+	Normal	Appendectomy	
5	100	—	Acute suppurative appendicitis	Appendectomy	
6	82	—	Normal	Suspension of uterus appendectomy, salpingo- oophorectomy, right	
7	62	—	Normal	Herniotomy, appendectomy	
8	58	+	Acute gangrenous appendicitis	Appendectomy	
9	52	+	Acute suppurative appendicitis	~Appendectomy	
10	45	—	Normal		
11	43	—	Normal	Resection of broad liga- ment and veins of left foot presacral nerve resection appendectomy, partial resection of right ovary	
12	40	—	Acute suppurative appendicitis	Appendectomy	
13	38	—	Acute suppurative appendicitis	Appendectomy	
14	35	+	Normal	Sterilization suspension of uterus, appendectomy hemorrhoidectomy	Pressure sustained to 35 cm; fecolith expelled; pressure dropped to 15 cm
15	20	+	Normal	Appendectomy, partial re- section of right ovary	
16	16	—	Acute gangrenous appendicitis	Appendectomy	
17	5	—	Acute suppurative appendicitis	Appendectomy	
18	4	—	Normal	Resection of terminal ileum, cecum, ascending colon and half of transverse colon	

Since the question under consideration is the role of increased intra luminal pressure as a factor in the pathogenesis of acute appendicitis for the purpose of this discussion all appendixes which showed no evidence of acute inflammation are classified as normal.



## RESULTS

In table 1, cases in which the appendix was perfused in situ are listed in the order of the initial resistance to perfusion. There were 3 appendices which resisted perfusion despite a pressure above 150 cm of water. All 3 showed appendicitis and contained fecaliths which were obstructing the lumen. At the other extreme, however, was a case (case 17) of acute suppurative appendicitis in which there was an initial perfusion resistance of only 5 cm of water. Between these two extremes, cases of acute appendicitis were observed in which the resistance pressures were 106, 56, 52, 40, 38 and 16 cm of water respectively.

On the other hand, the normal appendices in this series were almost evenly interspersed between the inflamed ones, with pressures of 134, 82,

TABLE 2—*Excised Appendices*

Case	Pressure, Cm	Cecum	Fecalith	Condition of Organ
19	150	Absent	+	Acute suppurative appendicitis
20	150	Present	+	Normal
21	150	Present	+	Acute suppurative appendicitis
22	150	Present	+	Normal
23	120	Present	+	Normal
24	150	Present	+	Normal
25	150	Present	+	Normal
26	120	Present	+	Normal
27	120	Present	+	Acute gangrenous appendicitis
28	110	Present	+	Normal
29	97	Present	—	Acute necrotizing appendicitis
30	95	Present	+	Normal
31	90	Present	+	Normal
32	90	Absent	—	Normal
33	76	Present	—	Normal
34	65	Absent	—	Acute gangrenous appendicitis
35	60	Present	—	Acute gangrenous appendicitis
36	57	Present	+	Acute gangrenous appendicitis
37	52	Present	—	Normal
38	44	Present	—	Normal
39	38	Absent	—	Acute suppurative appendicitis
40	36	Absent	—	Acute necrotizing appendicitis
41	35	Present	—	Acute gangrenous appendicitis
42	20	Absent	—	Acute gangrenous appendicitis
43	0	Present	—	Acute gangrenous perforative appendicitis

62, 45, 43, 35, 20 and 4 cm of water. None of the normal appendices sustained pressures as high as did those in cases 1, 2 and 3, in which acute appendicitis was present.

In table 2, cases in which the appendix was perfused after excision are listed in the order of the initial resistance to perfusion. In this group the absence of correlation between initial perfusion resistance pressure and acute inflammation is even more striking than with the appendices perfused in situ. Of the 7 appendices which resisted a pressure of over 150 cm of water, 4 were normal and 3 were acutely inflamed. In the remainder of the table the normal and inflamed appendices are fairly evenly dispersed, as they were in table 1.

In table 3 the cases in tables 1 and 2 are combined and arranged so that normal and acutely inflamed appendices are separated and listed in the order of their initial resistance to perfusion. In all cases of

resistance to pressures of 110 cm of water or more there were fecaliths obstructing the lumen. Of the 14 cases of this type, the appendixes in 7 were acutely inflamed, and those in the remaining 7 were not.

Of the appendixes in the remaining 29 cases, 7 had fecaliths. Of these, 4 showed acute appendicitis (57, 56, 52 and 20 cm of water respectively), and 3 were normal (90, 35 and 20 cm of water respectively). The remaining 12 were acutely inflamed, and 10 normal appendixes had no fecaliths.

In short, in the 43 appendixes in which the initial perfusion resistance pressure was measured there was no definite correlation between resis-

TABLE 3—*Initial Resistance to Perfusion of Normal and Inflamed Appendixes*

Acute Appendicitis		Normal Appendixes	
Perfusion Resistance Pressure, Cm	Fecalith	Perfusion Resistance Pressure, Cm	Fecalith
150	+	150	+
150	+	150	+
150	+	150	+
150	+	150	+
150	+	134	+
150	+	120	+
120	+	110	+
106	—	95	—
97	—	90	+
65	—	90	—
60	—	82	—
57	+	76	—
56	+	62	—
52	+	52	—
40	—	45	—
38	—	44	—
36	—	43	—
36	—	35	—
35	—	20	+
20	+	4	—
18	—		
5	—		
0	—		

tance to perfusion and the presence of acute inflammation. There was, however, good correlation between resistance to perfusion and the presence of fecaliths.

#### COMMENT

Wangensteen and Dennis<sup>1a</sup> have presented data from which they have concluded "It appears likely that the chief inciting agency in bringing about appendicitis in man is obstruction of an appendix in which the mucosa possesses the normal secretory capacity."

Since our data on the initial perfusion resistance pressure of the appendix as an index of intraluminal obstruction is not entirely consistent with their conclusions, it seems worth while to review their evidence in detail.

They studied 22 patients in whom the appendix was ligated at its base and exteriorized coincidentally with the performance of colostomy. In 5 of these there developed intraluminal pressures of 90 cm or more

or more in a manometer connected to a cannula tied into the tip of the appendix. All of these appendices had "good mucosa" in the control sections and gave microscopic evidence of "acute diffuse appendicitis" in sections taken after high intraluminal pressure had developed.

Of the remaining 17 cases, there were 4 in which no sections were obtained before obstruction and 14 in which no sections were obtained after obstruction.

There were 3 in which sections were obtained after obstruction. In case 9, in which there developed a pressure of 42 cm of water, there were no control sections, and the condition was reported as "mild acute diffuse appendicitis with exudate in the lumen" after obstruction. In case 17, in which a maximum pressure of 8 cm of water developed, there was no mucosa in the control section, but serositis and a few leukocytes in the muscle layer were observed after obstruction. Curiously enough, in case 20, in which there was no mucosa in the control section, there were mucus and leukocytes in the lumen, but no intraluminal pressure developed. No description is given of the muscularis or of the serosa to distinguish the condition in this case from "acute diffuse appendicitis."

This is the sum total of the evidence which Wangenstein and Dennis present as "experimental proof of the obstructive origin of appendicitis in man."

A critical analysis of these data suggests the following considerations.

1 Since in 14 cases there were no histologic studies of the appendix after obstruction of the lumen, no conclusions can be drawn as to whether the histologic picture of "acute diffuse appendicitis" was present in these (control?) cases.

2 Since the amount of appendix exteriorized was too short for biopsy in 64 per cent of all the cases studied, or 82 per cent of the "control" cases, it seems not unlikely that the specimens taken from those appendices reported to have acute diffuse appendicitis were taken very close to the point where the cannula was tied in. If this is so, the inflammatory change observed may well have been due to local injury of tissues in the neighborhood of the cannula and the ligature.

It becomes apparent, then, that from the data of Wangenstein and Dennis<sup>1a</sup> no definite conclusions can be drawn regarding the causation of appendicitis in man. This is particularly unfortunate, because such conclusions might have established the relation of appendicitis in the human being to the various types of appendicitis studied in animals by these investigators.<sup>1</sup>

Returning to the data presented in table 3 it is clear that a definite correlation does exist between high initial resistance to perfusion and the presence of fecaliths. It is possible then that in the 7 cases of acute

appendicitis in which high initial resistance to perfusion was found in the presence of an obstructing fecalith, secretion against obstruction may have played a role in the pathogenesis of the disease. On the basis of the available evidence this can be neither affirmed nor denied. However, in 13 cases in our series of 23 (table 3) in which acute appendicitis developed in appendixes with initial perfusion resistance pressures of 60 cm of water or less, fecaliths were present in only 4. This suggests strongly that secretion against obstruction is not the only mechanism for the development of appendicitis.

On the other hand, the finding of 7 normal appendixes which had initial perfusion resistance pressures of 110 cm of water or more and contained fecaliths is evidence that obstruction of the lumen does not necessarily cause appendicitis.

#### SUMMARY AND CONCLUSIONS

The "initial perfusion resistance pressure" was studied in 43 appendixes removed at operation and was correlated with the histologic observations.

Eighteen studies were done *in situ* and 25 immediately after appendectomy without clamping or handling of the organ.

The results were similar in the two groups and may be summarized together.

- 1 There is a definite correlation between high initial perfusion resistance pressure and the presence of fecaliths.

- 2 High initial perfusion resistance pressure due to obstruction by fecaliths may occur in the normal appendix.

- 3 While secretion against obstruction may be a factor in the pathogenesis of acute appendicitis, it is certainly not the only mechanism.

- 4 There was no definite correlation between resistance to perfusion and the presence of acute inflammation.

# FIBROSARCOMA OF SOFT TISSUE PRODUCING REGIONAL CONCENTRIC BONE ABSORPTION

ORMAND C JULIAN, M D  
CHICAGO

The relation between the usual type of soft tissue sarcoma invading bone and the resulting bony change is well recognized. Such a lesion is commonly a fibrosarcoma of the fascial plane which grows with moderate rapidity and produces ragged absorption of adjacent bone.

The case recorded here is that of a very slowly growing fibrosarcoma of the soft parts of the forearm which first affected the bones seven years after onset of the tumor. The morphologic structure of the tumor was such that its malignant character was not suspected from examination of tissue removed at the first operation and was never definite on the basis of histologic observations alone. The unusual nature of the bone lesion resulting from the sarcoma, the great length of the history of the tumor, the difficulty encountered in making the pathologic diagnosis and the results of the conservative therapy used owing to this difficulty make this case worthy of an individual report.

## REPORT OF A CASE

Mrs E B, a woman 43 years of age, was first seen at the Billings Memorial Hospital in January 1934. In 1922 she had fallen downstairs, hurting the left arm but sustaining no severe injury. One year later, in 1923, a small tumor was noted beneath the skin on the dorsal surface of the left forearm, about 3 inches (7.6 cm) above the wrist. The tumor grew slowly during the following years until 1930, when the central portion became indented. In July 1930 a roentgenogram of the forearm, taken because of this tumor, showed, as compared with the same region of the other arm, a sloping reduction in diameter of 3 cm of the shaft of the radius under the region of the tumor. No treatment was instituted, and very slow growth of the tumor continued, with only occasional slight discomfort in the region. A second roentgenogram, taken in June 1933, showed a more advanced diminution in circumference of the radius 2 to 3 inches (5 to 7.6 cm) above the wrist (fig 1).

On November 16 the patient sustained a fracture of both bones of the forearm at the level of the tumefaction. The arm was immobilized in a cast for eight weeks, but at the time of examination at the Billings Hospital, Jan 26, 1934, the fractures were ununited.

Coinciding with the fracture level there was seen an indurated umbilicated soft tissue tumor" of the skin and subcutaneous tissue of the dorsum of the

From the Department of Surgery of the University of Chicago

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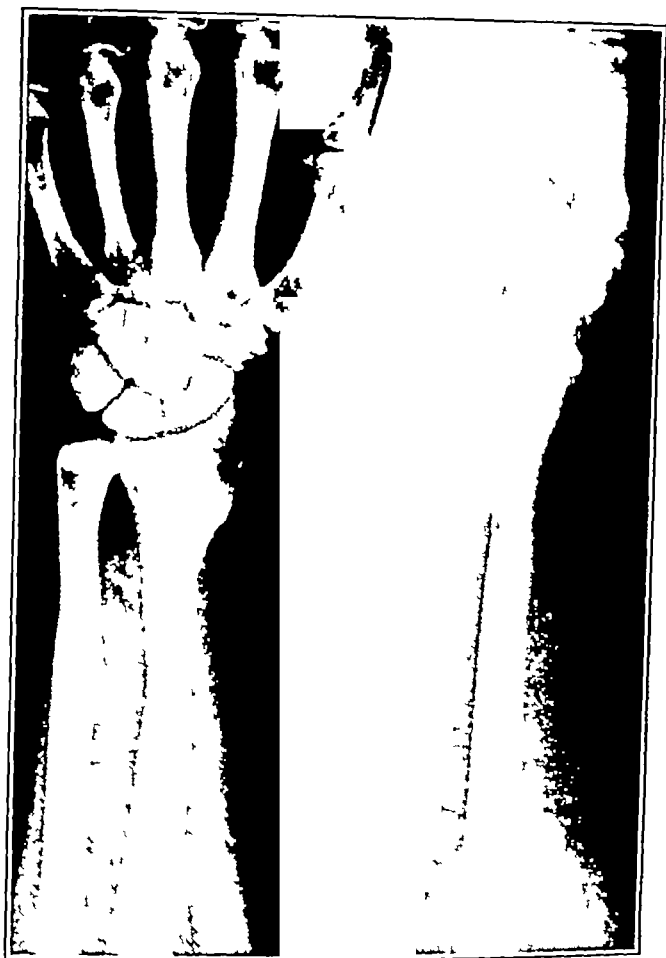


Figure 1

*(See legend on opposite page)*

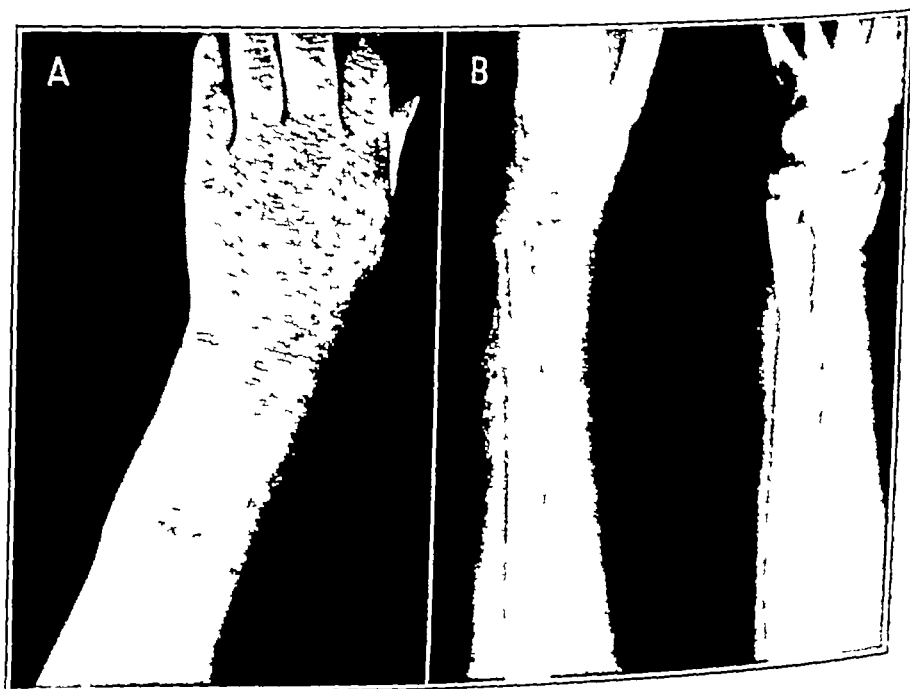


Figure 2

*(See legend on opposite page)*

forearm (fig 2 A) In a roentgenogram (fig 2 B) the radial fragments showed a 2 to 3 cm segment of moderate concentric absorption of the shaft, centering on the fracture line The ulnar fracture was at about the same level, but the fragments showed no absorptive change

Open reduction with bone grafting was performed on January 26 by Dr D B Phemister With the tumor of the soft parts excluded from the field, the radius was exposed at the fracture level through an anterior incision The shaft was found to be reduced nearly to one half of its normal diameter at the fracture site There was no peripheral callus or evidence of tumor on the fragment ends A small amount of callus between the bone fragments was curetted out, and a strip of periosteum 3 cm long was cut from the upper radial fragment Two full thickness bone strips from the right tibia were placed as onlay grafts, one anteriorly and one laterally After closure of this wound a large biopsy specimen was taken of the depressed lesion of the skin and subcutaneous tissue A cast was applied

*Pathologic Report*—The tissues were examined microscopically The section of skin and subcutaneous tissue taken from the depressed lesion contained a layer of thin squamous epithelium with little cornification The corium and the subcutaneous tissue were completely replaced by fibrous tissue This fibrous tissue in different areas varied in maturity and in cellularity In the more densely cellular regions (fig 3) the cells were large and were spindle and oval shaped, with dark chromatin and distinct chromatin-perichromatin differentiation No mitotic figures were present The cells were arranged in streams and whorls No palisading of the nuclei was evident The callus from between the fragments was histologically mature collagenic connective tissue, with several spicules of living cancellous bone The periosteal strip had a thin attached layer of cortical bone Along the entire surface was an interrupted line of periosteal new bone and more superficially a layer of condensed collagen, thickest near the fracture, which represented the callus stimulated by the fracture Dense, mature fibrous tissue (fig 4) was seen in contact with the cortical bone at the end away from the fracture This tissue had produced a broad, smooth indentation in the cortex Examination of the cortical edge from this region toward the fracture disclosed, beneath the traumatically stimulated callus and new bone, numerous lacunar spaces resembling Howship's lacunae in form but containing no giant cells The last-mentioned changes apparently represented the pathologic process which produced the concentric absorption noted in the roentgenograms taken before the fracture No tissue resembling tumor was present

The cast was removed on March 26, eight weeks after operation, and a roentgenogram showed bony union of the fracture A mild degree of concentric absorption of the ulna was then noted at the healed fracture site The "biopsy wound" of the depressed lesion had healed, but after a few months it broke down

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Fig 1—Roentgenogram showing reduction in the circumference of the radius (June 1933)

Fig 2—A, photograph of the arm two months after fracture with resulting nonunion, showing the tumor of the forearm and its depressed center B, fractures of both bones, sustained in November 1933 The radial fracture is through the narrowed region shown in figure 1

On November 7 a deep ulcer was present in the indurated zone on the dorsum of the forearm. The hard edge of the ulcer was narrow and the base crusted. Biopsy material from the base and edge was taken on this date.

A section taken from this biopsy tissue contained a segment of skin which was normal to the abrupt, unelevated edge of a shallow ulcer. The floor was



Fig. 3—Photomicrograph of a less mature area in the scarred subcutaneous tissue. The tissue was taken at the time of the first bone grating.

covered by a superficial thin layer of necrotic tissue, beneath which the subcutaneous tissue was replaced by very immature connective tissue. The cells of the tissue were round and spindle shaped and formed invading whorls and strands.



occupying the immediately subcutaneous tissue and extending in some areas into the subcutaneous fat. One definite mitotic figure was seen (fig 5).

Because the results of biopsy suggested malignancy, excision of the entire field of the ulcer and the indurated areas was done on December 3. A full thickness pedicle graft was applied to the area after excision of the lesion. At operation

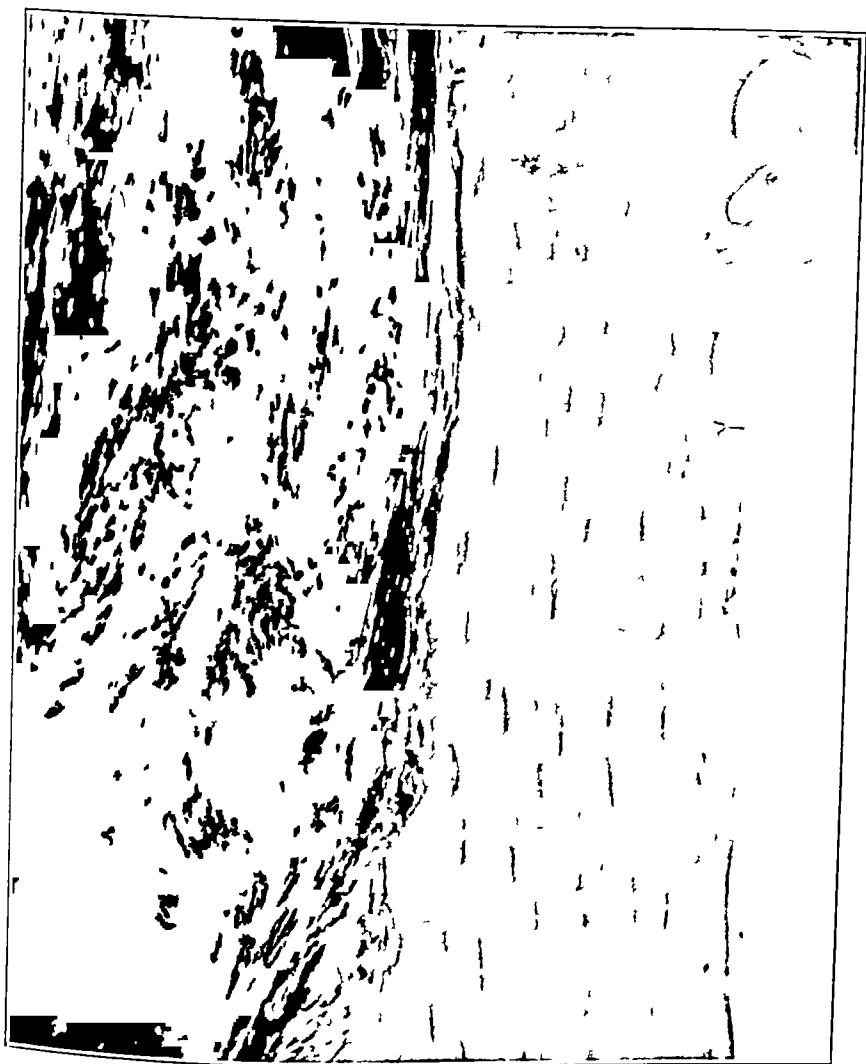


Fig 4—Photomicrograph of the proximal end of a piece of periosteum, showing dense, nontumorous fibrous tissue encroaching on the cortex of the radius.

grayish, nodular tissue was found invading the subcutaneous tissue. It extended down to the ulna and was dissected off the tendons and ulna, some tissue being left behind.

*Pathologic Report*—Gross Observations The specimen consisted of a piece of skin and subcutaneous tissue 5 cm square, in the center of which was a granulating ulcer 1.5 cm in diameter, having narrow, hard walls. The underlying subcutaneous tissue was indurated. There were several fragments of hard, nodular



Fig 5—Photomicrograph of an area in the subcutaneous tissue, showing a single mitotic figure (from the biopsy specimen of skin taken on Nov 7, 1934)

trabeculated tissue which had been dissected from the subcutaneous and intertendinous regions. Two nodules measured 2 by 1.5 by 1.5 cm and 3 by 1 by 0.5 cm respectively. On cross section they presented a smooth, pale, densely fibrous surface.

*Microscopic Observations* Sections were taken of the skin, the edge of the ulcer and various regions in the nodular tissue beneath. The epidermis at the

normal thickness in the region examined. There was a mild inflammatory infiltration in the narrow necrotic border of the ulcer. The superficial layers of the dermis showed densely collagenous scar tissue with sparse normal spindle cell nuclei. However, below the dermis a different type of connective tissue was seen. Here the cells, which formed nodular whorls and streams, varied tremendously in size, density of chromatin and shape. These cells in the subcutaneous tissue infiltrated from below the more superficial "normal" scar tissue in several places. Only three or four mitotic figures were seen in several sections of this invading type of tissue. However, the pleomorphism, immaturity and hyperchromatism suggested a slowly growing sarcoma. Sections of the deeper nodules contained the same pleomorphic tissue.

The wound healed by the end of January 1935, and no sign of recurrence was observed grossly. However, in March several scattered nodules suggesting sar-

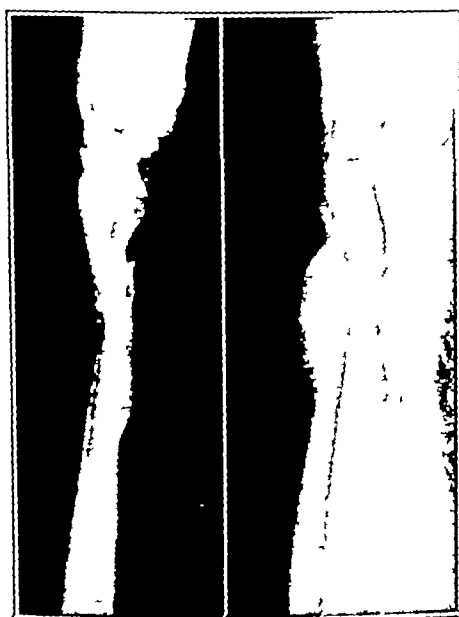


Fig 6—Roentgenogram taken in October 1936, showing the ulnar fracture in a region of marked concentric absorption. The radial graft is united. The soft tissue shadow shows the position of the full thickness skin graft.

coma appeared in the skin and subcutaneous tissues over the side and front of the radius. No axillary metastases could be felt.

Roentgen therapy was given from March to July, 1935. A single dorsal portal on the forearm received 5,038 r. By June the subcutaneous nodules had disappeared owing to the radiation therapy.

The patient remained free of symptoms and signs of recurrence until October 1936, when she began to have a recurrent painless clicking sensation in the ulnar side of the forearm at the site of the old fracture. A roentgenogram showed considerable sclerosis of the reconstructed radius. The radius was intact. The ulna was fractured in the center of a region of extensive concentric absorption (fig 6). At this time several cutaneous nodules had recurred. Biopsy specimens

were taken and showed tissue of the same morphologic character as that seen in the edge of the ulcer already described

Roentgen therapy (735 r) was given again at the end of October 1936. A roentgenogram taken in March 1937 showed further absorption of the ulnar fragments leaving a gap between the ends. The patient returned on May 24, complaining of pain in the forearm and loss of function of the wrist, the radius having been refractured through the grafted region. The patient was readmitted to the hospital for operation.

Operation was done on May 26. No callus was seen in the fracture region. The tissues about the bone were scarred, but there was no gross evidence of tumor. A 4 inch (10 cm) tibial bone graft and several cancellous bone chips were placed at the fracture level. After closure of this wound a second incision was made over the back of the ulna. A fracture of the ulna with spindle-shaped absorption of the ends of the fragments was found. The periosteum, which was thickened over the lower fragment, was reflected from both fragments. Beneath the periosteum of the lower fragment there was grayish tissue which looked like a thin layer of sarcoma. This was excised. No tumor tissue was found in the corresponding region of the upper fragment, but a strip of periosteum from here and several pieces of callus-like tissue from the fracture line were taken for examination. A whole thickness tibial graft and cancellous bone chips were applied at the fracture level.

Microscopic examination was made of all tissue removed. The bone chips and callus from the radius showed no tumor. The section of periosteum from the ulna showed various changes compatible with a weak attempt at healing of the fracture. The callus which was seen in the section showed only slight beginning calcification and no ossification. There was no definite evidence of sarcoma tissue in the region, which represented a segment of periosteum of the upper fragment  $1\frac{1}{2}$  inches (37 cm) long. The section made of the gray tissue found on the distal ulnar fragment contained tissue similar to the infiltrating tissue seen in the biopsy specimen previously studied. The cells showed enlargement and variation in size and definite hyperchromatic staining of the nuclei. No mitotic figures were seen in the sections studied.

When the cast was bivalved, on July 26, an ulcer of the skin 5 cm in diameter was found to have developed medial to the pedicle skin graft, exposing the deep fascia. Clinically, fibrous union of the fracture and grafts had occurred. A roentgenogram showed the grafts and fragments in good position, but there was no definite bony union. The ulcer remained unhealed despite removal of the pressure caused by the cast, and dead portions of the tibial grafts of the radius and ulna were sequestered during the following months. Two small nodules recurred on the back of the hand in March 1938, biopsy specimens were taken.

*Pathologic Report*—Gross Observations. The specimen consisted of a spindle-shaped piece of skin and attached subcutaneous tissue. Nothing abnormal could be seen on the surface of the skin, but on palpation one could feel a nodule in the subcutaneous tissue which seemed to be less than 0.5 cm in diameter.

Microscopic Observations. The section was through skin and subcutaneous tissue. In the depth of the subcutaneous tissue there was a small, roughly rounded lesion. This lesion was composed of large, somewhat atypical cells having round and oval nuclei. The nuclear pattern was distinct in most of the cells. There were no mitoses. The central portion of the lesion had been replaced by a pink-staining hyaline tissue which continued peripherally for a short distance into the cellular portion of the nodule as pink-staining fibers. There were no giant cells.

in the lesion. The periphery was surrounded by a collar of normal lymphocytes. There was no capsule to suggest that the tissue was an invaded lymph node. There was no invasion of the surrounding tissue. The general appearance of this lesion was that of a chronic granuloma. The central portion, however, on close exami-

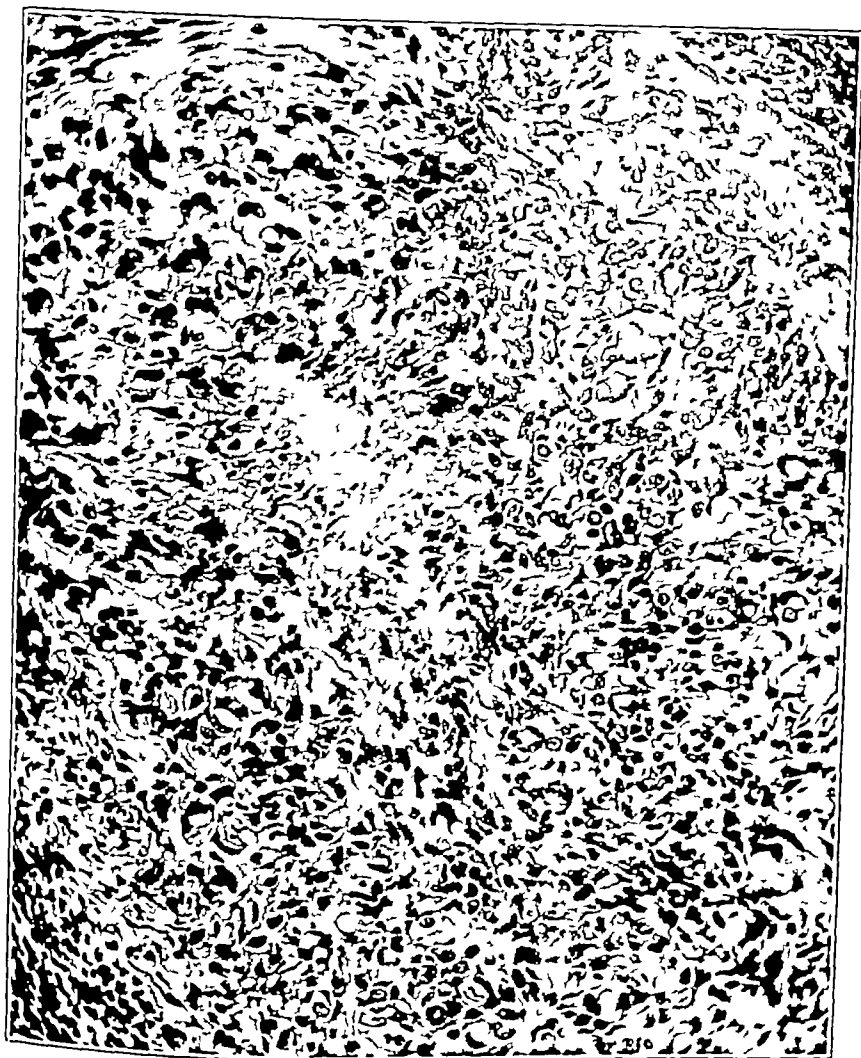


Fig 7.—Nodule in the subcutaneous tissue of a nodule from which a biopsy specimen was taken in March 1938. Note the central hyalinized portion and the continuation of the hyaline fibers out into the peripheral portion of the lesion.

nation was seen to be composed of hyaline fibers (fig 7) and not of necrotic material. Acid-fast stain of this section showed no organisms.

The hand was now almost completely functionless, and a roentgenogram taken in June 1938 revealed a complete fracture of the radius at the same level as the previous fractures. The radial graft distal to the fracture line was absent, hav-

been sequestered. The graft proximal to the fracture was firmly united to the shaft.

On July 5 the arm was amputated  $1\frac{1}{2}$  inches (37 cm) above the condyles of the humerus.

*Pathologic Report*—Gross Observations. The specimen consisted of the left forearm, the elbow and the distal 3 inches (7.6 cm) of the humerus. Four centimeters above the radiocarpal joint there was an ulcer measuring 4 by 2.5 cm over the dorsal radial surface of the forearm. Its edges were shiny, white, scarred and firmly attached to the underlying bone. The floor of the ulcer was a surface of bone. This bone appeared to be dead. Over the interosseous area, forming the ulnar border of this large crater, there was a full thickness graft which was firmly healed in place except where it bordered on the ulcer already described and in two small areas on the lateral side, where breaking down had occurred. The subcutaneous tissue about the ulcer and graft was markedly fibrous and was frozen to the underlying bone. There was a linear scar at the level of the condyle of the radius in which there was a hard shotty nodule measuring about 0.75 cm. Three smaller nodules were palpable in the skin of the dorsum of the hand. These were small and superficial, projecting above the skin. The forearm was narrowed at the level of the ulcer.

The bones of the forearm, when stripped of all soft tissue, presented very irregular surfaces. The radius was fractured directly beneath the soft tissue ulcer. This fracture showed no attempt at healing. Extending from this fracture proximally for a distance of 5 cm there was a solidly united portion of bone graft. The distal one fourth of this graft appeared white and dead, a sharp transverse groove being present at the junction between the living and the dead bone. The distal fragment of the radius was narrowed as it approached the fracture line, the fragment appeared to be alive.

The ulna was markedly thinned for a distance of about 4 cm, centering on the point opposite the radial fracture. In this narrowed region the medullary cavity of the bone was completely obliterated by dense bone. The remaining grafted bone had remained united, and its boundaries were indistinguishable on the uneven surface of the ulna.

Microscopic Observations. The sections included the various nodules on the back of the hand, the nodule found in the cutaneous scar at the elbow, portions of the scar tissue from the region of the fractures and sections of the bone constituting the distal 18 cm of the radius and the distal 9 cm of the ulna.

The radial segment was sectioned in two parts. They showed the articular end, a long portion of the shaft with fracture and a totally fused portion of a bone graft on the proximal fragment. This graft represented the proximal segment of the first graft applied. Its distal end formed the proximal part of the bony floor of the ulcer crater seen in the gross specimen. Microscopically, the articular cartilage of the distal radial articulation was replaced completely by fibrocartilage. The articular cortex of the bone was thin and in some places incomplete. The atrophic cancellous bone of the distal end of the shaft was composed of thin, widely spaced trabeculae. The marrow here was fatty. The cortex at the distal end was thin but rapidly became thicker proximally, where it assumed a grossly abnormal architecture. The bone retained its lamellar pattern, but the trabeculae were thick and branching. Some of these were composed of acellular bone. Fatty marrow near the distal end of the radius was invaded by irregular masses of anaplastic round and oval cells arranged in whorls and streams (fig 8). Fi -

cells had laid down a small amount of collagen and had stimulated a fibrous tissue reaction about them of normal adult fibroblasts. One or two mitotic figures were seen in the sections examined. This same tissue was present in one large area on the surface of the radius over the region of invaded medullary canal.



Fig 8—Photomicrograph of a section of the radius in the amputated specimen. The medullary cavity is invaded by tumor tissue. Several spicules of dead cancellous bone are in the field.

The graft was seen to be firmly fused with the shaft of the proximal fragment of the radius. The graft itself was composed of cortical bone, some of which was acellular. The medullary spaces of the graft were filled predominantly by fibrous tissue, but a few areas showed invasion by tumor. The distal end of

the graft, which was exposed in the soft tissue ulcer, was entirely dead bone. It showed the changes of acute osteomyelitis. The ulnar segment resembled the radius in atrophy and regions of replacement of fatty marrow by tumor tissues. A portion of the bone in the region of

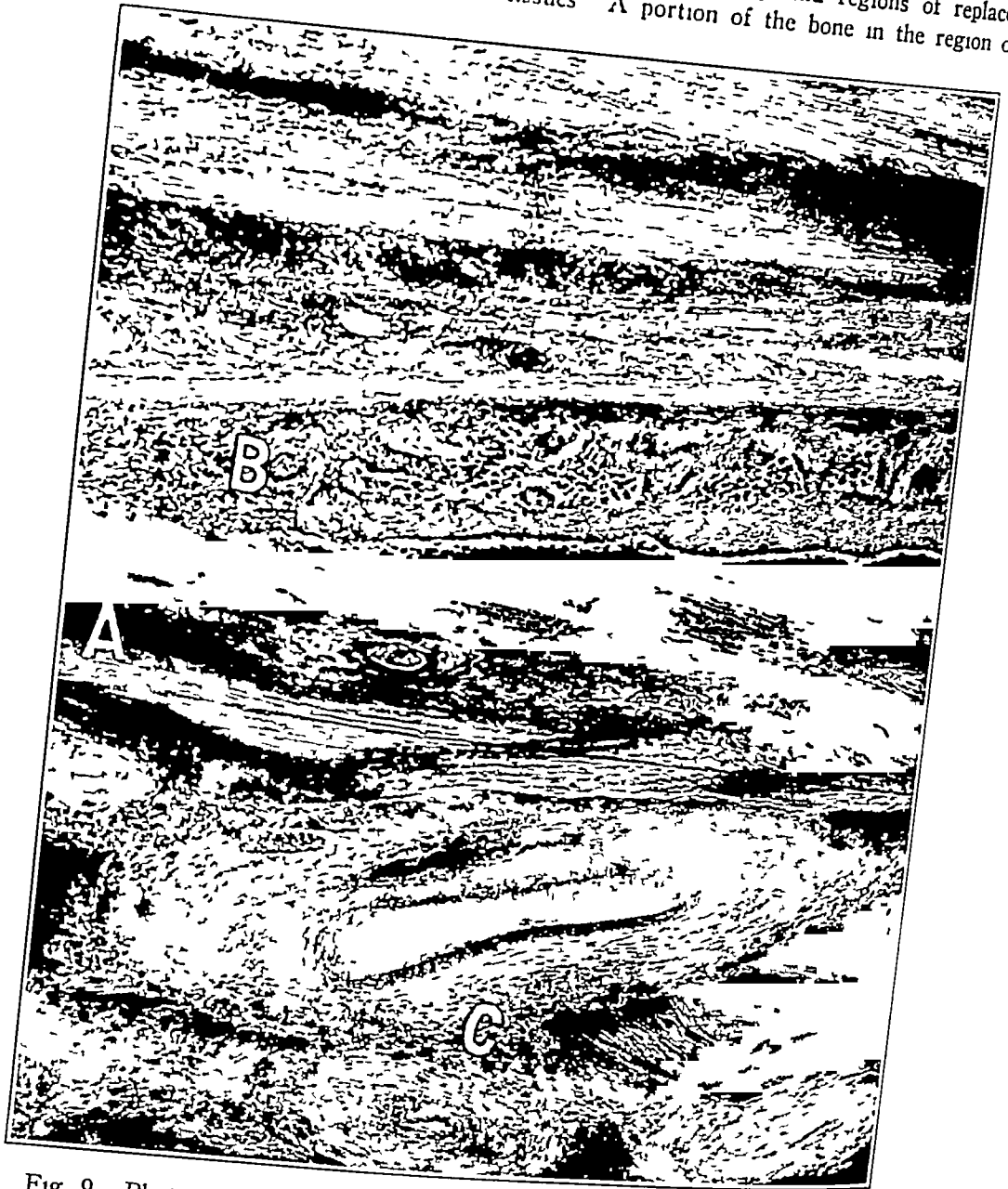


Fig 9—Photomicrograph of the cortex of the ulna and scar tissue on its surface taken from the amputated specimen. *A*, cortex of the shaft, *B*, periosteal new bone with tumor tissue in the intertrabecular spaces, *C*, fibrovascular tissue in the medullary spaces, showing marked giant cell absorption of bone.

the fractures and bone grafting contained no medullary cavity and appeared to represent a completely assimilated bone graft.

A short segment of periosteal new bone was present on one surface of the ulna (fig 9). The tissue in the spaces between the trabeculae of this new bone was indistinguishable from the invading tumor tissue seen within the bone.



Sections of the cutaneous nodules showed small collections of sarcoma tissue in the superficial portion of the subcutaneous tissue. The tissues taken from the firm, scarred region about the radius and ulna contained very dense collagenous connective tissue with frequent infiltrates of tumor cells.

After operation, the humeral stump healed without event.

In January 1939, a small, nontender, firm nodule was noticed in the upper third of the scar in the right leg (fig 10). This nodule was only 0.5 cm in diameter, and because it was situated exactly in the incision it was considered to be scar tissue. However, its center became depressed, forming an umbilicated



Fig 10—Depressed surface of the tumor nodule which developed in the scar of the right leg

though not ulcerated lesion. It was excised in March and revealed immature fibrous tissue similar to that seen in various other nodules and tissues already examined. This wound healed rapidly and at the time of this report shows no evidence of recurrence.

The tendency of this tumor to attack the skin was again observed in November, when a tiny nodule was found in the scalp. On excision the same low grade sarcoma tissue was seen. Several more nodules then appeared in the scalp and were treated in February 1940 by application of radium.

At the time of the present report the patient is free of local recurrence but is receiving roentgen therapy to the scalp to supplement the radium therapy.

## COMMENT

The diagnosis in this case is slowly growing fibrosarcoma of the soft parts of the arm with an unusual type of concentric absorption of the bones. At first operation there was no gross or microscopic evidence of tumor at the fracture site or on the surface of the fragments.

The late appearance of a sarcomatous lesion in the wound in the leg is of great interest when one considers the sequence of surgical procedures of the operation during which the graft was taken from this region. The tumor of the soft parts had been excluded from the incision in the arm, and the only tissue handled which gave possibility of transplant was that about the radial fracture. This tissue showed neither gross nor microscopic evidence of malignancy. However, the fact that sarcoma tissue was almost certainly transplanted from the fracture site throws considerable doubt on this evidence.

The histologic structure of the cutaneous nodules, of the various tissues removed at operation and of the tissue invading the bones found after amputation was not in itself diagnostic of a malignant neoplasm but rather suggested an immature fibroma.

The possibility of a leprous infection was suggested by the roentgen appearance of the forearm, and one of the cutaneous lesions strongly suggested a chronic granuloma (fig. 8). Acid-fast stains of several of the tissues gave negative results.

The cause of the primary osteolytic process in the radius is obscure, though malignant disease was suggested by the transplant already described. It might be explained on a basis of vascular changes associated with the growth of a tumor in the immediate vicinity.

Osteolytic changes following trauma, with or without fracture, are well recognized. However, the so-called post-traumatic painful osteoporosis (Sudeck's atrophy) is most frequently seen in the hands and feet and takes the form of generalized moth-eaten osteoporosis of a region and not that of concentric absorption of a short segment of bone.

Recently, several cases reported by French authors<sup>1</sup> have been grouped as examples of essential osteolysis. In these cases there was very slowly progressive, usually concentric, absorption of a segment of the skeleton. In all except 1 the lesion was preceded by a history of trauma. In those in which the patients were operated on, no definite tumor was found. Bone grafting, done in 2 of these cases, gave results comparable to those obtained in my case. The lesion extended to the

1 Radulesco, A. D. Un cas curieux d'osteolyse complete de l'extremite inferieure, *J. de radiol. et d'electrol.* **21** 304, 1937. Mouchet, A., and Rouvillois, H. Osteolyse du bassin d'origine indetermine, *ibid.* **21** 263, 1937. Dupas, J., Badelon P., and Dayde, G. Aspects radiologiques d'une osteolyse essentielle progressive de la main gauche, *ibid.* **20** 383, 1936.

graft in each case and produced concentric absorption. No vascular, endocrine, metabolic, hereditary or inflammatory factor was found in these cases, but a neoplastic process could not in any case be ruled out.

#### SUMMARY

A case covering a seventeen year history of slow concentric absorption of both bones of the forearm is presented. The diagnosis was made of soft tissue fibrosarcoma of very low grade malignancy. This was supported by the finding of cutaneous metastases. Other possible diagnoses—granuloma, notably leprosy, Sudeck's atrophy and so-called essential osteolysis—are discussed.

# REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, MD  
LOS ANGELES

FRANK HINMAN, MD  
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, MD  
BUDAPEST, HUNGARY

ALEXANDER B HEPLER, MD  
SEATTLE

ROBERT GUTIERREZ, MD  
NEW YORK

GERSHOM J THOMPSON, MD  
AND

JAMES T PRIESTLEY, MD  
ROCHESTER, MINN

EGON WILDBOLZ, MD  
BERNE, SWITZERLAND

AND  
VINCENT J O'CONOR, MD  
CHICAGO

## KIDNEY

*Anomaly*—MacKenzie<sup>1</sup> reported a case in which two separate clinical entities occurred in the same organ, namely, cystic inflammation of the pelvis and ureter and embryonic defect or lack of development that had occurred during intrauterine life

Cystic disease of the urinary tract is primarily a disease of old age, occurring in persons of either sex from whom a history of disturbance or definite inflammation of the urinary tract can be elicited. The condition is reported to have occurred in several cases of double ureter, and, as in MacKenzie's case, it may occur in conjunction with congenital renal hypoplasia.

MacKenzie admitted that proliferative renal fibrosis and chronic pyelonephritis with interstitial and glandular degeneration as encountered in his case may be termed "renal atrophy." However, his assumption was that these changes represent secondary atrophy superimposed on hypoplasia, the latter being purely congenital in origin.

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1 MacKenzie, D W. Renal Hypoplasia with Pyelitis Cystica and Ureteritis Cystica. Report of a Case and Review of the Literature, Tr Am A Genito-Urin Surgeons 32 321-335, 1939

Smith<sup>2</sup> reported 8 cases of horseshoe kidney. Two of the patients were not operated on, 2 underwent left nephrectomy for hydronephrosis, 3 underwent pyelolithotomy and 4 underwent division of the isthmus. Symptoms of pressure by the isthmus on the great vessels were exhibited by 2 patients. The need for investigation of the blood supply before division of the isthmus is done was emphasized. Smith did not advise division of the isthmus in patients who show no signs or symptoms of pressure on the great vessels but stated that such patients should have the benefit of repeated excretory urograms for a period of years to insure against the development of renal damage. If such patients are found to have stones or hydronephrosis, the isthmus should be divided when the operation for stone or hydronephrosis is done.

**Tuberculosis**—Randall<sup>3</sup> reported a case of bilateral renal tuberculosis of thirty-seven years' standing and of known and proved existence from the time the patient was 18 years old to the time of the report, when the patient was 55. At the time of writing the patient weighed 190 pounds (86 Kg) and had every appearance of enjoying perfect physical health. Actually no vesical symptoms were observed, but at intervals of two to three months the passage of renal calculi caused fever, pain and occasionally hematuria.

In explaining the unusual latency and delay of progress of the disease, Randall stated that the responsible organism may be of low virulence or the resistance of the host extremely high. But he expressed the belief that there is a basically distinct difference in renal balance when the two organs, each of normal development, are simultaneously affected to an equal degree by disease or obstruction. While he was studying by means of urograms the silent unilateral renal death which occurs when malignant tumor of the bladder gradually occludes one ureteral orifice, Randall observed cases in which the renal response was different when both ureters were equally obstructed from the response noted when only one ureteral orifice was occluded. When one ureteral orifice was occluded, its kidney quietly ceased to function, and the opposite kidney carried on bodily functional needs without symptomatic complaint or physical change. But in cases in which the two ureters were about equally involved, pictures of extreme response to necessary bodily demands were observed, and bilateral hydroureters and hydronephroses of increasing degrees pictured nature's efforts and the renal response to fight to the last ditch, so to speak, and to the ultimate point of renal counterbalance before allowing these vital organs to fail.

2 Smith, G. G. Surgery in the Horseshoe Kidney, *Tr Am A Genito-Urin Surgeons* 32: 73-83, 1939.

3 Randall, A. Bilateral Renal Tuberculosis. A Unique Case, *J Urol* 43: 35-38 (Jan) 1940.

Randall expressed the belief that in the case of bilateral renal tuberculosis which he reported there was evidence of nature's compensatory efforts to carry on vital function when the two organs are equally involved, for it was impossible for either organ to shift its burden and functional responsibility to an uninvolved mate

De Langre<sup>4</sup> reported a case in which renal tuberculosis was associated with cysts of the kidney in a girl 16 years of age. The patient had never had any renal or vesical symptoms until pyuria had made its appearance, one and a half years prior to her examination by De Langre, and it had been discovered in the course of a general examination for a state of fatigue. *Mycobacterium tuberculosis* subsequently was found in the patient's urine, and nephrectomy was performed for a tuberculous right kidney. Examination of the specimen revealed the presence also of a number of small cystic cavities and tuberculous granulations.

On the basis of what Roubier, Cibert and Barral wrote in 1935, only 6 cases of this kind appear to have been found in the literature. The case discussed here differed slightly from the others, in all of which there were true polycystic kidneys. The kidney in the present instance contained numerous cysts but was not much increased in size, and the cysts were small, being properly termed microcysts of the kidney rather than the type commonly observed in polycystic kidneys. The pathogenesis of such cysts, however, is not clearly understood. The designation "cysts of nephritis" is well suited to those found in the kidneys of elderly persons or in kidneys affected by chronic nephritis, but the patient in De Langre's case was very young and had never shown any signs of having had nephritis earlier. Nor does it appear that tuberculosis was the cause of the cysts in De Langre's patient. All kinds of transitional stages could be observed, in fact, from cysts with smooth walls, invested with endothelium, to cysts with granular seeds on the wall and cysts transformed into tuberculous caverns. The tuberculosis in this case was clearly secondary, grafted on the cysts. The hypothesis of renal malformation, comparable to that of polycystic kidney, is much more acceptable as an explanation of the mode of formation of such cysts than is tuberculosis.

The other kidney of De Langre's patient appeared to be perfectly sound, it could not be palpated, and the pyelogram of the pelvis and calices showed them to be normal. The case confirms the conclusion reached by Roubier, Cibert and Barral that tuberculous lesions may become grafted on a preexisting polycystic kidney.

Keyes<sup>5</sup> discussed closure of the wound in the loin without drainage after nephrectomy for tuberculosis. Of the patients from whom he

4 De Langre. Tuberculose et kystes du rein, *J d'urolog* **47** 138-140 (Feb) 1939

5 Keyes, E. L. The Closure of the Loin Wound Without Drainage After Nephrectomy for Tuberculosis, *Tr Am A Genito-Urin Surgeons* **32** 33-37, 1939

removed tuberculous kidney and who survived and were followed for more than a year after operation, clamps had been left on the pedicle in 13. Four of these died of tuberculosis or renal insufficiency. Two of them were alive at the time of his report but had tuberculosis three and five years, respectively, after operation. One was active and well twenty-four years after operation. Seven were well when they were last heard from.

Of the 9 patients who underwent drainage without clamps and who were followed, 3 were dead of tuberculosis six, six and thirteen years, respectively, after operation. One had died of embolus. Two patients were alive and had tuberculosis five and twelve years respectively after operation, and 3 were well respectively eight, eleven and twenty years after operation.

Of the 23 patients treated by suture without drainage and followed 10 were dead of tuberculosis, and 13 (more than half) were alive and well, at the time of the report.

Keyes stated that as a result of this experience he was impressed with the theory that after nephrectomy for tuberculous kidney the drain in the loin is a site of mixed infection and sinus formation in the loin. If the sinus opens after complete closure, this fact need not imply a tempestuous or a prolonged convalescence. Drained tuberculous wounds today do well, undrained wounds do better. Keyes expressed the belief that the results of modern atraumatic surgical technic will be better than his were since the last war, namely, 20 of 23 wounds in the loin closed without any drain whatever, and two sinuses formed, only one of which was a grave one. He stated that since surgeons are no longer timid about tying the renal artery, it is not necessary to be timid about closing the tuberculous loin.

Rathbun<sup>6</sup> stated that in all cases in which definite dense, hard strictures at the lower end of the ureter are present in the widely dilated ureter, complete ureterectomy should be done in addition to nephrectomy. There are some cases in which, for one reason or another, ureterectomy is rather a formidable procedure.

Rathbun expressed the belief that, no matter how careful aseptic technic may be, a certain number of bacteria are injected into every wound that is made. He wrote that nature takes care of such bacteria pretty well if allowed a reasonable chance to do so, but any incision in the loin is a highly traumatizing operation, with much bruising of the muscles and the like. Much serous exudate forms, and an outlet should be provided for such exudate, otherwise pressure necrosis may occur,

<sup>6</sup> Rathbun, N. P., in discussion on papers of Randall, Howard and Keyes, *Tr. Am. A. Genito-Urin. Surgeons* 32: 42, 1939.

which sets the stage for infection. A simple cigaret drain inserted at the dependent angle of the incision and removed in forty-eight hours certainly should not do any harm, if one proviso is carefully observed. The dressing should be done with the same painstaking, aseptic technic that characterized the operation.

Deming<sup>7</sup> stated that there are three principles concerning incisions made in operations for tuberculous kidneys which should be kept in mind by urologic surgeons. The first is that all tuberculous tissue should be removed. Deming advocated removing the whole ureter with the kidney. The second is that protection of the incision should be afforded as far as injury to the walls is concerned. The third is a surgical principle which some surgeons forget—complete drainage of the incision. Not all incisions are dry. In cases in which the incisions are wet a drain left in position for forty-eight or seventy-two hours relieves the wetness of the incision. General surgical experience tells the urologic surgeon that a dry incision heals far better than does a wet incision. Deming had not had any incision break down during the nine years prior to his discussion. The fact that resident surgeons in the service were able to obtain equally good results shows, Deming stated, that the three principles which he mentioned have some merit.

Colby<sup>8</sup> stated that for persons in whom the lower end of the ureter is strictured or in whom the ureter is much dilated he removes the ureter completely. In most of his cases, however, the ureter is simply treated by means of phenol and ligation.

None of the patients is operated on until he has been in the sanatorium for from two to six months. The low incidence of complete breakdown of incisions is in contrast to the incidence of such breakdowns among persons who have had their kidneys removed without the benefit of previous sanatorium treatment. Possibly, the same thing may be true of similar incisions in patients operated on for diseased ureter, in other words, the patient's resistance to this disease is brought to a considerably higher level by means of sanatorium treatment. Patients placed in a sanatorium previous to operation certainly do better after operation. In only 1 instance in Colby's experience in the last six or seven years was it thought necessary to remove a ureter which had been left in place after nephrectomy. This ureter was removed because the patient had persistent pain in that side, and about 6 inches (15 cm.) of atrophied ureter was removed, in which there was no microscopic evidence of tuberculosis.

<sup>7</sup> Deming, C. L., in discussion on papers of Randall, Howard and Ketch, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 44, 1939.

<sup>8</sup> Colby, F. H., in discussion on papers of Randall, Howard and Ketch, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 43-44, 1939.



*Tumor*—Wharton<sup>9</sup> stated that the diagnosis of early renal tumor must occasionally be based on the general clinical picture or on suggestive evidence, in spite of the absence of any single infallible sign.

When there is presumptive evidence of renal tumor, the proper treatment is exploration.

Clinical data must be accurate and interpreted with judgment, in order that mistakes may be avoided. It is, however, a more serious error to postpone an operation until the situation is clear than it would be to perform an exploratory operation and find no hypernephroma. The decision requires the exercise of fine judgment, and the surgeon who saves lives occasionally will explore and find no tumor. Generally, however, some pathologic condition is present which will explain the bleeding, such bleeding rarely is idiopathic.

It is usually impossible to distinguish a benign cyst from a hypernephroma, and it is usually unsafe to presume that such a distinction can be made.

Preoperative irradiation also may confuse the picture in a questionable case and should be reserved for proved tumors.

The lumbar route is preferable to the transperitoneal route for surgical exploration of a kidney. The transperitoneal operation is indicated in cases in which the presence of a tumor has been established and in which the situation lends itself to this procedure.

Barney<sup>10</sup> reported a case in which extrarenal hypernephroma afflicted a white man 70 years of age. General examination, including the making of pyelograms, showed that a huge, partially calcified tumor was occupying the lower pole of the right kidney. At operation it was found that the tumor extended up under the costal margin. The tumor was somewhat necrotic and was markedly adherent to the lower pole, from which, however, it could be separated. The kidney was not removed. The diagnosis was hypernephroma. The patient died four years after the operation, at which time necropsy disclosed no evidence of metastatic disease.

Cahill<sup>11</sup> elaborated on two points in Barney's paper concerning extrarenal "hypernephromas." First, the term "hypernephroma" has been applied to tumors of a definite gross and microscopic appearance. These tumors definitely and frequently occur in the kidney, and they have been reported as a rare occurrence in the adrenal body and in

9 Wharton, L. R. Hypernephromas That Are Too Early to Diagnose, *J Urol* **42** 713-719 (Nov) 1939.

10 Barney, J. D. Extrarenal Hypernephroma, *Tr Am A Genito-Urin Surgeons* **32** 47-56, 1939.

11 Cahill, G. F., in discussion on papers of Barney, Kretschmer and Smith, *Tr Am A Genito-Urin Surgeons* **32** 85-87, 1939.

adrenal rests Adrenal rests are found in the retroperitoneal tissues anywhere from the adrenal region to the testes or the ovary

In a careful review of roentgenograms of all the renal tumors which had been seen in the Squier Clinic, it was found that calcification shadows occurred in the tumor in 22 per cent of cases The first published discussion of renal calcification was a paper on renal tumors written by Braasch At that time, based on results obtained at the Mayo Clinic, Braasch thought that calcification permitted a rather favorable prognosis However, Cahill stated that a review of reported cases led to the opposite conclusions A study of large numbers of tumors characterized by calcification will show more conclusively whether calcification of the tumor has any special effect on the prognosis Calcification apparently is secondary to necrosis or hemorrhage Cahill also has found that calcification is a valuable sign in distinguishing solitary cysts from round tumors, depending on the appearance of the calcified deposits

Nowlin<sup>12</sup> reported 2 cases in which 2 brothers died of malignant tumor of the kidney One brother was 67 years old and had undergone left nephrectomy, with recovery Death occurred two months later from pulmonary metastasis The histologic picture was typical of hypernephroma In the case of the other brother, 62 years old, the diagnosis was made by cystoscopy and urograms He refused all treatment and died shortly afterward from pulmonary metastasis

*Calculi*—Gutierrez<sup>13</sup> drew attention to the vital problems presented by bilateral nephrolithiasis, which in the past was frequently regarded as definitely inoperable but for which the indications for operation today are known to be wider and the prognosis more favorable than ever before Nevertheless, determination of the indications for surgical intervention and the operative management is still a difficult and serious task, requiring experience and the knowledge gathered from observation of many individual patients There is no single rule, each patient must be treated according to the particular conditions present

The frequency of bilateral nephrolithiasis is greater than has been supposed, it has been variously estimated to constitute from 6 to 20 per cent of all instances of renal stone The mortality rate is more than double that accompanying the unilateral condition, the destructive pathologic process having always the tendency to destroy the entire renal parenchyma, with consequent complete loss of function In addition, the maintenance of latent infection ultimately leads to anuria and terminal uremia

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12 Nowlin, P Familial Tendency to Renal Carcinoma, *J Urol* **43** 654-655 (May) 1940

13 Gutierrez, R Surgical Treatment of Bilateral Nephrolithiasis, *Urol & Cutan Rev* **43** 642-652 (Oct) 1939

Early diagnosis is of great importance, but unfortunately the silent course of the disease in many cases causes the patients to come late for surgical relief, and the fact that the well advanced lesion is bilateral may make a fatal outcome inevitable. Nevertheless, in every case in which nephrolithiasis is of moderate extent, the condition should be considered potentially operable. Cases in which no operation is permissible are those in which renal function is inadequate or in which the urogram reveals the presence of too little cortical parenchyma for restoration of function. Even in such cases, however, exception must be made of certain cases of calculous anuria and far advanced pyonephrotic kidney, since emergency nephrostomy performed for drainage may succeed in prolonging somewhat the life of the patient.

Among the most important types of bilateral nephrolithiasis are those in which (1) a stone lies in the pelvis of each kidney, (2) both stones are of the staghorn type, (3) there is a stone in each kidney and one in one ureter, (4) the stone is in an anomalous kidney, perhaps a double kidney, on one side and in a normal kidney on the other, (5) the nephrolithiasis is in polycystic kidneys, and (6) the stone is in a horseshoe kidney. In addition to those, many other types exist, each of which calls for experienced judgment in the choice of an operation.

Diagnosis is made by roentgenograms, pyelograms and cystoscopic examination. Functional tests are essential, as are also an estimation of the amount of urea in the blood and the making of cultures. A roentgenogram which depicts the kidney as normal does not exclude the presence of certain types of stones, which may be revealed only by a filling defect in the pyelogram.

Gutierrez reported 6 of his own cases to illustrate the different problems that may be encountered in the surgical management of the condition under discussion. These bring out the importance of proper preliminary preparation and adequate postoperative treatment of the patient to attain permanent cure and to prevent recurrence. Two of the cases show the clinical confusion which exists in diagnosis, especially when secondary anemia is the conspicuous symptom, with the stone running a silent course. Three cases (reported through the courtesy of colleagues) illustrate bilateral coraliform stones afflicting patients who came too late, because of too advanced disease and poor general condition, for operation. These 3 cases serve to emphasize the need of recognition of such conditions before they become hopeless.

The surgical risk and operative mortality rate depend on the judgment of the surgeon as to the advantageous time to operate, a judgment which should be based on renal function, the urea content of the blood and the general condition of the patient. The right choice of a procedure, the rapidity with which it is carried out, the type of anesthesia employed and the preoperative and postoperative care all will play a part in the outcome.

The fundamental principle in these cases is to operate whenever it is possible, first on the better kidney, with a view to having this organ in good condition in the event that it is found advisable or practicable to perform nephrectomy on the other kidney. For the same reason it is always best to operate first on the kidney in which the stone is free in the pelvis and is smaller and hence more easily removed by simple pelviolithotomy or nephrolithotomy. The power of a kidney to regain its function is so remarkable that the principle of conservation is essential in treatment of surgical conditions arising in this system. The duty of the surgeon to save a kidney whenever possible cannot be too strongly stressed.

When a kidney contains multiple calculi, has fairly good function and is not pyonephrotic, it is important, after it has been surgically exposed, to examine it fluoroscopically and to make roentgenograms to rule out definitely the possibility that stones or fragments may have been left in any of the calices or in the renal parenchyma, since these "forgotten fragments" not only actually jeopardize the condition of the kidney but stimulate recurrence and infection, which may result in the formation of a subsequent renolumbar fistula and in the persistence of renoureterovesical infection.

When renal calculi are larger than the normal caliber of the ureter and cannot pass spontaneously or by means of cystoscopic and ureteral manipulations, the most common operations required are pelviolithotomy, nephrolithotomy, pelvionephrolithotomy, nephrostomy, calicystectomy, heminephrectomy, nephrectomy and ureteronephrectomy, the choice depending on the type of lesion and the condition of the individual patient.

For obtaining curative results, the maintenance of lumbar drainage after any type of conservative operation on an infected lithiasic kidney by means of a supplementary nephrostomy tube is of the greatest practical importance. Furthermore, mere surgical removal of the stones from the kidneys by no means constitutes adequate treatment for calculi, since in the modern concept of the relief and cure of these conditions post-operative care for the purpose of securing drainage, relieving infection and preventing recurrence is one of the most important requisites.

Oppenheimer<sup>14</sup> recommended operative roentgen control (roentgen study of the surgically exposed kidney) as a valuable aid in the operative treatment of renal calculi. In his series, in 29 (34 per cent) of 85 examinations performed under operative roentgen control, stones or fragments of stones which could not be palpated or found without the roentgenogram were located by means of it and were removed.

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14 Oppenheimer, G. D. Evaluation of Roentgenography of Surgically Exposed Kidney in Treatment of Renal Calculi, *J. Urol.* **43** 253-264 (Feb) 1940.

Kearns<sup>15</sup> stated that in many instances the recurrence of stones is preventable if proper study is applied to causative factors. Application of the definite advances achieved in chemotherapeutic measures designed to combat infection alone will result in a diminution in the incidence of reformation of stone.

A fundamental requisite to proper preventive treatment lies in the administration of vitamin A, augmented by all the other vitamins for their synergistic action. Partial deficiency of vitamin A is a real possibility as a factor in the development of recurrent stones. Some persons have capricious appetites and others have an aversion to certain essential foods. Still others, because of their economic status, are deprived of these elements, in some, faulty assimilation results in varying degrees of deficiency.

During the thirteen years prior to the time of his report, Kearns recommended vitamin A in the diet for the prevention of recurrence of urinary calculosis. During this period, among all the calculous patients observed by him, it was possible to follow a group of 164 who adhered to their dietary instructions. This group included all patients who either passed stones spontaneously or underwent surgical or cystoscopic removal of stone. It included also patients with and without infection. There were only 8 instances of recurrence, or 4.8 per cent. A large number included those who were uninstructed, who failed to follow treatment or who were untraced. An intake of water of 60 fluidounces (about 1,800 cc) daily is advisable to promote mechanical flushing and to insure ample water for solubility of urinary solids.

**Trauma**—Domrich<sup>16</sup> reviewed cases reported in the literature of blunt traumatism of the kidney. He reported 55 cases and came to the following conclusions:

The only indications for primary nephrectomy are severe hemorrhage and extensive destruction of the kidney. In a number of cases in which conservative treatment is carried out surgical intervention will be necessary later. Bleeding is the most serious complication and infection the second most severe. Half of Domrich's patients whose kidneys did not heal had infection of the urinary tract later. Hydronephrosis, ureteral stricture and renal stones are the most common late complications of trauma. The stones apparently form around a nucleus of a blood clot. Nephrectomy is the most common operation. Perinephritic abscess which develops after hemorrhage may be drained and the kidneys left intact. Patients who have undergone nephrectomy usually obtain good results and are capable of doing their usual work. Indus-

<sup>15</sup> Kearns, W. M. The Prevention of Recurrence of Urinary Stone, *J. Urol.* 43: 598-610 (April) 1940.

<sup>16</sup> Domrich, H. Die stumpfen Nierenverletzungen und ihre Folgezustände *Ztschr. f. Urol.* 33: 337-381, 435-465 and 521-541 1939.

trial accident commissions and insurance companies should take this lack of long-continued symptoms into consideration in the adjustment of these cases

*Denervation*—Wildbolz<sup>17</sup> reviewed the literature on denervation of the kidney and discussed the results of his own experiments on dogs and also his clinical experience. He found that all the nerves to the renal parenchyma enter at the renal hilus. A denervated kidney eliminates a greater number of solid substances than does a healthy kidney. Clinically, the best method for denervation of the kidney is mechanical destruction of the nerves situated along the renal hilus. Wildbolz and Schneider showed that this can be done by animal experimentation. They found also that the flow of blood through the denervated kidney is 60 to 100 per cent higher than the flow of blood through a normal kidney. The effects of denervation last about six months.

Wildbolz also discussed the clinical results obtained in 61 cases. Denervation is useful only in those cases in which the underlying pathologic process can be cleared up during the six months in which the effect of denervation persists. Results are most satisfactory in cases of acute nephritis, which endangers the life of the patient by anuria or which may develop into chronic nephritis. Results are also good with hematurias of unknown origin. If, after surgical exploration, conditions are found in the kidney other than those expected, denervation should not be done, since it might possibly cause harm. This operation is definitely not a panacea for diseases of the kidney, but in its proper place it is a very useful procedure.

*Aneurysm of the Renal Arteries*—McClelland<sup>18</sup> discussed aneurysm of the renal artery, of which trauma is the most common cause. A history of a previous injury or of contusion of the kidney usually is obtained, and later the signs and symptoms of the aneurysm appear. Arterial disease itself, causing degenerative changes, such as those associated with arteriosclerosis, periarteritis nodosa and syphilis, favors the formation of aneurysm.

Hematuria, pain, swelling and pulsation are the usual symptoms. There may be a slowly growing swelling in the flank. The growth is progressive and is accompanied with a dull throb over the mass. In a few instances a systolic bruit occurs over the mass and is diagnostic. Hematuria may appear weeks or months after the original injury.

Mathé stated that in only 7 of 56 reported cases was the condition diagnosed or suspected before death of the patient or operation. The roentgenogram is of great value. A ring shadow denser at its periphery

17 Wildbolz, E. Ueber die Denervation der Niere, *Schweiz med Wchnschr* 69 825-829 (Sept 16) 1939.

18 McClelland, J. C. Aneurysm of the Renal Artery, *Tr Am A Genito Urin Surgeons* 32 169-175, 1939.

and situated at the hilus of the kidney is diagnostic. A pyelogram will show this shadow to be entirely separate from the pelvis or the major calices. It may be situated directly between the two major calices.

Thirty-five of 56 untreated patients died. Seventeen of 21 patients operated on were saved from certain death by removal of the kidney. Death occurs as a result of exsanguination and is usually caused by hemorrhage into the peritoneal cavity, around the kidney or into the urinary tract. Most of the patients die within a year from the onset of the swelling and pain.

Operation should be performed as soon as the aneurysm is suspected. The true aneurysm is treated by nephrectomy through an incision in the flank.

*Infection*—Nesbit and Dick<sup>19</sup> stated that acute staphylococcal infections of the kidneys are relatively common. They are hematogenous in origin, the lesion being cortical and showing a tendency to heal promptly and completely.

Costovertebral pain, tenderness and fever are constant. The urine rarely contains pus, but the stained sediment reveals cocci. Secondary bacillary infection of the urine frequently occurs. The disease tends to run a stormy, although self-limiting, course, ending in complete recovery.

Surgical complications occur in approximately 10 per cent of cases, and the appearance is heralded by an increase in symptoms and signs. These complications, perinephric abscess and carbuncle of the kidney, are readily diagnosed at onset and should be treated by immediate drainage. Pulmonary complications of perinephric suppuration occur in 16.5 per cent of cases and often cause delay in diagnosis and treatment of the underlying pathologic lesion. Such complications regress under adequate treatment of the underlying subdiaphragmatic disease.

*Abscess*—Jeck<sup>20</sup> reported 2 cases of large solitary abscess of the kidney. In only a few of these cases was the condition recognized pre-operatively.

One of Jeck's patients was a man in whose case a tentative diagnosis of perinephric abscess was made. No free pus was found around the kidney. A fluctuating region was detected on the posterior curvature of the kidney and was opened. Two fluidounces (59 cc) of heavy pus was evacuated.

In the other case the patient, a woman 27 years old, had marked tenderness in the left costovertebral angle. She had a definite sensation of fullness in the left loin. The kidney was exposed through an oblique

<sup>19</sup> Nesbit, R. N., and Dick, V. S. Acute Staphylococcal Infections of the Kidney, *J Urol* **43** 623-636 (May) 1940.

<sup>20</sup> Jeck, H. S. Large Solitary Abscess of the Kidney, *J Urol* **43** 28-34 (Jan) 1940.

incision in the loin The perinephric fat was very pale The kidney itself also was very pale and appeared to be somewhat enlarged and rather firm In the upper half of the kidney, on the posterior surface, well up under the ribs, was felt a fluctuating region about the size of a half-dollar, and while an attempt was being made to separate the upper pole, a finger was accidentally passed into this region, which immediately released a large quantity of yellowish, fairly liquid pus The cavity from which the pus came was then explored digitally and apparently did not communicate at all with the renal pelvis As far as could be estimated, the cavity had contained 3 to 4 fluidounces (88 to 118 cc) of pus, and its walls were smooth

A history of boils, carbuncles, paronychia, acute osteomyelitis, infected teeth, infected tonsils or other, similar foci of infection is of the utmost importance in establishing a diagnosis when other signs point to the kidney With all such infections chills are usually found to be followed by the spiking type of increased temperature, pain in the loin of the affected side, more or less tenderness about the infected kidney, a moderately high leukocyte count, a low erythrocyte count with a low hemoglobin percentage and, finally, a rather marked loss in weight

The treatment of large solitary abscess of the kidney is incision and drainage On exposure of the kidney when abscess is suspected, if the abscess is not at once apparent, decapsulation of the kidneys should be performed, for, as Beer has pointed out, a solitary abscess or multiple abscesses may not be discovered until the true capsule of the kidney is removed

*Perirenal Abscess*—Hamer<sup>21</sup> stated that perinephritic abscess of extrarenal origin in most cases is the result of blood-borne infection to the renal cortex followed by cortical abscess with extension to the perirenal tissues The source of the infection is some remote focus, such as a carbuncle, a boil, an infected wound, or an infection of the respiratory tract Calculous disease and tuberculosis are the most common causes of perinephritic abscess of renal origin

The infecting organism is usually one of the pyogenic coccus group

The chief symptoms are pain and tumor in the loin, with costovertebral tenderness, fever of the septic type and severe leukocytosis

Diagnosis in the early stages is most difficult Urologic study is of value in cases of primary renal disease, but in most cases of the metastatic condition positive urologic evidence is lacking

Roentgenograms may show a clouded renal region, obscuration of the border of the psoas muscle and scoliosis

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21 Hamer, H G Perirenal Abscess, Surg, Gynec & Obst 70 595 597 (Feb 15) 1940



The value of thorough drainage is emphasized. With the metastatic type of abscess simple drainage is usually followed by prompt recovery. For the type of abscess which is secondary to existing renal disease nephrotomy or nephrectomy may be required. Nephrectomy usually should be postponed until drainage has relieved the patient of his sepsis.

*Nephrostomy*—Moore<sup>22</sup> presented a method providing for immediate nephrostomy with the continued use of the same tube as an internal support of the ureter but without the undesirable feature of prolonged external nephrostomy drainage. This method should encourage prolonged splinting of the ureter after any type of operation on the ureteropelvic junction, since the tube can be retained without disturbance of the patient in any way. This procedure was used for 5 patients operated on for hydronephrosis. Moore also described a tube designed to eliminate the inadequacies of the ordinary rubber tube.

*Nephrotomy*—Higgins and Glazier<sup>23</sup> discussed the relative merits of the scalpel and the high frequency current as employed in nephrotomy. In their experimental work they studied histologically the relative amount of primary hemorrhage, the intrarenal extravasation of blood along the lines of incision, the infarction of renal tissue and the relative rate of healing.

They concluded that less primary hemorrhage occurs when extensive nephrotomy is performed with the cutting current than when a scalpel is used. Extravasation of blood into the renal tissue adjacent to the line of incision is greater when the scalpel is used. There is less infarction adjacent to the line of incision when the high frequency current is employed. Healing is more or less similar with the two methods.

*Nephropexy*—Young<sup>24</sup> discussed his technic for nephropexy, in which he employs decapsulation and suture of rolled-up capsule to muscles of the back. His technic has a twofold purpose: (1) to decapsulate the posterior surface of the kidney, so that firm adhesions between the substance of the kidney and the muscles of the back may be secured, and (2) to utilize the rolled-up edges of the capsule on each side of the decapsulated region as strong material around which sutures can be passed which hold the kidney against the muscles of the back. The capsule is divided along the midline of the posterior surface of the

22 Moore, J. G. A New Procedure for the Correction of Ureteropelvic Junction Obstruction, *Pennsylvania M. J.* **43** 631-634 (Feb.) 1940.

23 Higgins, C. C., and Glazier, M. Relative Merits of the Scalpel and High Frequency Current in Nephrotomy. Experimental Study, *Tr. Am. A. Genito-Urin. Surgeons* **32** 9-18, 1939.

24 Young, H. H. Nephropexy. A Technique Employing Decapsulation and Suture of Rolled-Up Capsule to Muscles of Back, *J. Urol.* **43** 20-27 (Jan.) 1940.

kidney The capsule is stripped off and rolled up, and the sutures are placed along the inner border and then along the outer border Heavy chromic sutures are used, and the needle is then passed up through the psoas muscle about 2 cm from the bodies of the vertebra

*Results of Nephrectomy*—Hanley<sup>25</sup> reviewed the postoperative results of nephrectomy There were, altogether, 213 histories Of the 182 patients traced, 100 actually were examined clinically, and their renal function was estimated

The 213 patients whose histories were reviewed were placed in six groups, according to the original diagnosis hydronephrosis, pyonephrosis, calculus, tuberculosis, neoplasms, and an unexpected diagnosis, chronic nephritis

There were 40 cases in which nephrectomy had been done for simple hydronephrosis without any evidence of infection, the operations having been performed from two to six years prior to the time of Hanley's report Twenty-nine patients were traced The operative mortality rate for the group was 5 per cent, 2 deaths occurred within a fortnight of operation The total mortality rate was 10 per cent, there being 2 additional deaths within two years of operation, both of the patients dying in uremic coma No more deaths had occurred in this group during the four years prior to the time of writing

There were 44 operations for pyonephrosis during the previous two to six years Only 4 patients were untraced The operative mortality rate was 20.2 per cent, 9 patients dying within a month of operation, 1 from pulmonary embolism The total mortality rate for this group was 34 per cent, 6 additional deaths occurred during the following two years One of these deaths followed nephrolithotomy two years after nephrectomy No more deaths occurred in this group during the four years prior to the time of writing

There were 49 cases in which nephrectomy for calculus was performed during the two to seven years prior to the time of the report Forty of the patients were followed up The operative mortality rate was 6.1 per cent, with 3 deaths The total operative mortality rate was 16.3 per cent, with 5 additional deaths, all of which occurred within two years of nephrectomy except the death of 1 boy, who died five years after operation for a nonrenal condition

Nephrectomy was done in 48 instances for supposedly unilateral tuberculosis of the kidney and was performed during the two to eight years prior to Hanley's report Forty-two of the patients were followed up The operative mortality rate was 4.1 per cent, with 2 deaths The total mortality rate at the end of six years had increased to 22.9 per cent

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25 Hanley, H G The Post-Operative Results of Nephrectomy, *Brit J Surg* 27 553-566 (Jan) 1940

Nephrectomy was performed in 27 instances for new neoplasms. The operative mortality rate was 22.2 per cent, 6 patients dying within a week of operation. The total mortality rate within the next two years increased to 63 per cent, 9 patients dying within thirteen months of the operation and another 2 within two years of operation.

There were 5 patients whose kidneys after removal showed evidence of chronic nephritis, with no histologic evidence of any other pathologic process. The operative mortality rate was 20 per cent, with 1 death occurring eight days after operation. The total mortality rate was 100 per cent, all the patients dying within eight months of nephrectomy. Since chronic nephritis is a progressive and bilateral condition, it is only to be expected that the mortality rate should be high. In none of these cases was there anything to indicate the true nature of the pathologic process before operation.

#### URETER

*Anomaly*—Crenshaw<sup>26</sup> added new cases to those reported by him in 1935. He reported 6 cases of aberrant ureter with extravescical orifices (bringing his total to 13 cases), 3 new cases of abortive ureteral development (totaling 5 cases), and a second case of crossed ureteral ectopia. Another case of multiple calculi in an extrapelvic cystocele is reported.

Crenshaw summarized certain data concerning the 13 cases of aberrant ureter with extravescical orifices. In 12 of the cases the patients were females. Four were children. In all but 1 case the pelvis was duplicated, and all the aberrant ureters came from the upper part of the pelvis. There was 1 case of bilateral duplication with bilateral extravescical orifices, necessitating bilateral heminephrectomy. The excretory urogram does not readily outline the abnormal pelvis, frequently because of reduced renal function in the anomalous upper segment of the kidney, instead, dependence on an elongated renal shadow with a disproportionate amount above the upper calix of the lower segment is significant. Retrograde pyelographic examination of the lower segment cannot always be depended on. Urethroscopic examination may reveal the aberrant orifice, but this orifice is not always easy to find and is not necessary for establishment of a diagnosis. Cystoscopic examination should be made to determine that only the two normal ureteral vesical orifices are present. Heminephrectomy resulted in cure in all cases.

<sup>26</sup> Crenshaw, J. L. Ureter with Extravescical Orifice. Supernumerary Ureter Ending Blindly, Crossed Ureteral Ectopia, Stones in Extrapelvic Cystocele, Report of Eleven Cases, *Tr Am A Genito-Urin Surgeons* 32:133-155, 1939, *J Urol* 43:82-101 (Jan) 1940.

The 3 new instances of abortive ureteral development were incidental discoveries encountered during study of patients who were undergoing cystoscopic or urographic examinations for other reasons. No patient required any treatment.

In the second instance of crossed ureteral ectopia the patient was an 8 year old boy who had numerous other congenital deformities. Urologic studies revealed a solitary (right) kidney opening into the left side of the bladder by a dilated ureter. The right ureteral orifice was not present. Nephrostomy on the right side relieved the patient of his symptoms.

A cystocele following hysterectomy prevented complete emptying of the bladder in a 54 year old woman. Vaginal repair with vaginal cystostomy and removal of calculi resulted in satisfactory recovery.

*Calculi*—Ormond<sup>27</sup> stated that ureteral calculus in each case presents the following questions: Is immediate operation desirable? If not, should manipulation be tried? If so, what method should be used? How long is it safe to temporize?

Each surgeon must be guided by his own experience, judgment and skill. Ormond has come to the conclusion that only the less drastic forms of manipulation are indicated. Patients who have stones the expulsion of which cannot be stimulated by gentler measures should be operated on after a sufficient period has passed for the stones to be expelled. Such a period will be measured by the amount of disability caused by the pain and by careful evaluation of the damage produced. Ormond has seen a stone lodged in the lower part of the ureter expelled after six months of careful observation. This stone caused in that time only four days of disability to the patient and no appreciable damage to the kidney. Some patients treated by multiple manipulations have been subjected to more danger, have suffered more pain and have lost more time than if they had been operated on in the first place.

In all cases, whether operation is done or not, attempts to prevent recurrence should be made. Ureteral dilation, pelvic irrigation, treatment of infection and attention to diet, to fluid intake and to changing urinary reactions usually will prevent recurrence.

Thompson and Kibler<sup>28</sup> reported 361 cases in which ureteral calculi were manipulated transurethrally. Approximately an equal number of patients were treated expectantly, and a similar number (392) were treated surgically. Cases in which simple diagnostic ureteral catheterization was carried out were not included.

<sup>27</sup> Ormond, J. K. Complications and Dangers of Lower Ureteral Calculi, *Gynec & Obst* 70 584-587 (Feb, no 2A) 1940

<sup>28</sup> Thompson, G. J., and Kibler, J. M. Treatment of Ureteral Calculus, with Reference to Transurethral Manipulation, *J. A. M. A.* 114 6-12 (Jan 27 1935) 553-556

Anuria and uremia are the only indications for emergency treatment. Time and sedation will relieve many patients of their stones, but the type of treatment employed must be individualized. Whether manipulation should be done depends on the size of the stone, the size of the ureter, the position of the stone in the ureter and ready access to the ureter from below. Manipulation should be performed in the hospital with the patient under anesthesia. Manipulation usually is done through either the Braasch cystoscope or the McCarthy panendoscope by the following instruments: (1) multiple catheters, (2) Councill extractor, (3) the Johnson extractor, (4) a spiral stone dislodger and (5) the Collings knife. Postoperatively, two ureteral catheters are passed to the pelvis and left in place for forty-eight to seventy-two hours to obviate development of obstructive edema. Roentgenograms made postoperatively will demonstrate whether all of the stone has been removed.

In 330 cases (91.4 per cent) the results were immediately or subsequently successful. In 4 cases (1.1 per cent) the result was complete failure. In 27 cases (7.5 per cent) elective or essential surgical treatment was administered for removal of the stone after attempted manipulation. An average of 1.26 manipulations was necessary for each case in which the procedure was successful.

Serious fever developed in 2.7 per cent of patients after removal of the indwelling ureteral catheters. These patients responded to reinsertion of the catheters or to the intravenous administration of mercuriochrome (the disodium salt of 2,7-dibromogammahydroxymercurifluorescein). In 8.8 per cent of the patients mild reactions occurred. Severe complications were rare. One patient died after manipulation and surgical treatment, death being referable to a massive pulmonary embolus which developed while the patient was satisfactorily convalescent. A short period of hospitalization is one of the main advantages of transurethral removal of ureteral calculi; 75 per cent of the patients remained in the hospital less than one week. Failures and complications cause an occasional prolonged stay. The economic factor should not cause the surgeon to try too forcefully to succeed. Absence of evidence of renal function on the affected side is valueless in the presence of an impacted ureteral calculus. Excretory urograms taken several weeks later may show a normal pelvic outline.

O'Connor<sup>29</sup> discussed prostigmine methylsulfate as an aid in the expulsion of ureteral calculi.

The original dosage recommended by Hager (10 cc of a 1:2,000 solution [0.5 mg of the active substance injected subcutaneously]) of

<sup>29</sup> O'Connor, V. J. Prostigmin as an Aid in the Expulsion of Ureteral Calculi, *Tr Am A Genito-Urin Surgeons* **32**: 185-191, 1939.

prostigmine methylsulfate at three to four hour intervals for four doses) is still the most satisfactory. O'Connor used this dosage in the treatment of 52 patients. Seventeen of these patients received from two to four series of injections. The selection of patients for nonsurgical treatment was made with the usual recognition of the problem presented by each patient.

In 16 cases ureteral meatotomy, ureteral dilation and insertion of multiple catheters or bougies were employed, with the injection of sterile olive oil, papaverine hydrochloride and the like, without dislodging or producing passage of the stone. In the knowledge that the lower part of the ureter was capacious and in the absence of complications which would call for surgical intervention, prostigmine was administered, with resultant rapid downward progress or expulsion of the calculus in 12 of the 16 cases. In 9 cases the calculi passed within twenty-four hours after the injection of prostigmine methylsulfate. In 2 patients a second course of injections administered after a three day interval resulted in expulsion of the stone in eight hours and fourteen hours, respectively. One patient passed three large calculi after a third course of prostigmine methylsulfate, no cystoscopic treatment having been administered for three months. The calculi had remained in the same position, as determined by roentgenograms, for a period of eighteen months.

Two patients passed multiple calculi after receiving injections of prostigmine methylsulfate when both manipulative and surgical attempts at removal had been unsuccessful. During the period of this survey (twenty-three months) 13 patients were relieved of ureteral calculi by operation, and for 1 of the aforementioned patients operation was unsuccessful. Seven other patients were treated successfully without resort to injections of prostigmine methylsulfate. Thus, in summary concerning 66 patients treated, prostigmine methylsulfate was used as an additional aid in the treatment of 52, and in 18 of these the clinical response was so direct and so obvious as to establish in O'Connor's mind without any reasonable doubt, the virtue of this medicament.

*Injury*—Hyman and Wilhelm<sup>30</sup> reported 5 cases in which ureteropelvic anastomosis was established after avulsion, with a discussion of the procedures necessary for successful results in such establishment.

They stated that reimplantation of a ureter severed from the renal pelvis, either accidentally or in the treatment of obstructive hydronephrosis, is based on the following principles: (1) provision of free urinary drainage by means of nephrostomy, (2) accurate suture of the

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30 Hyman, A., and Wilhelm, S. F. Ureteropelvic Anastomosis Following Avulsion, *J. Urol.* **43**: 52-60 (Jan.) 1940.

ureter to the pelvis without tension and (3) splinting of the anastomosis with a catheter to immobilize the ureter and to maintain the stoma

It is generally agreed that nephrostomy should be performed in all cases in which any extensive plastic procedure is done on the pelvis or the ureter. The tube acts as a safety valve, preventing undue internal tension on the plastic suture lines. Free drainage is the first requisite in the treatment of urinary infection, from which most of the patients under consideration suffer.

On the basis of their experience with plastic operations on the pelvis for obstructive hydronephrosis as well as their experience in cases of ureteral avulsion, the authors expressed the belief that prolonged drainage is often desirable.

Anastomosis between the ureter and the pelvis should be established with accurate apposition of the parts. When possible, it is preferable to suture the mucosa and the muscularis in separate layers and to use fine interrupted plain catgut sutures for the mucosa and fine interrupted chromic sutures for the outer layers.

A straight splinting ureteral catheter, inserted into the severed ureter for about 10 cm and brought out through the renal pelvis and cortex, facilitates anastomosis. It also serves the double purpose of splinting the ureter and maintaining the stoma. Although this catheter is a foreign body, its advantages appear greatly to outweigh its drawbacks. Too early removal of this catheter may result in stricture or in complete occlusion of the stoma. The splinting catheter should be left in place for at least ten days.

Late stricture not uncommonly follows reimplantation of a severed ureter into the pelvis. Frequent examinations should be done by excretory urographic methods. Any narrowing at the ureteropelvic junction is an indication for prompt cystoscopic dilation.

*Transplantation*—Lower<sup>31</sup> stated that transplantation of the ureters into the rectum or the sigmoid flexure in the presence of the congenital deformity exstrophy of the bladder has been practiced for many years. The length of time for which a child could live in comfort after undergoing such a procedure before dying from infection in the upper part of the urinary tract did not seem of as much concern as the comfort such a child would enjoy during life and the lessening of the care he would need. It soon became apparent that a child would probably live as long after this procedure as if no surgical treatment for exstrophy had been given, if not longer. Sufficient time has now elapsed in a series of cases large enough to permit evaluation of this procedure and to enable

<sup>31</sup> Lower, W. E. Transplantation of the Ureters into the Rectosigmoid and Cystectomy. Motion Picture Demonstration, Tr. Am. A. Genito-Urin. Surgeons 32:163, 1939.

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31 Lower, W. E. Transplantation of the Ureters into the Rectosigmoid and Cystectomy. Motion Picture Demonstration, Tr. Am. A. Genito-Urin. Surgeons 32:163, 1939.

urologic surgeons to apply it to the treatment of other conditions, such as malignant processes in the urinary bladder, intractable interstitial cystitis, tuberculosis of the bladder and (in certain instances) vesicovaginal fistulas

Lower exhibited a motion picture of a technic which he has adopted and which has simplified the procedure and reduced the operative mortality rate. To the date of his report, his series consisted of 105 cases, the operation having been performed for various anomalies and pathologic conditions of the urinary bladder. He followed the patients and found that a majority of those living were entirely free from symptoms and that renal function was good even after many years had elapsed. One woman became pregnant and was delivered of a healthy child by cesarean section three years after undergoing ureteral transplantation, other patients have carried on their various vocations and have worked in perfect comfort.

*Intussusception*—Bumpus<sup>32</sup> reported a case in which intussusception of the ureter afflicted a man 52 years old. The renal stone was removed, after which the patient experienced further trouble. Urograms and ureteral catheterization revealed what appeared to be intussusception of the ureter, a condition which Bumpus construed to be caused by a fragment of stone which had remained in the ureter. The ureterogram showed definite intussusception of the lower segment of the ureter into the upper. Subsequent passage of the stone and disappearance of ureteral torsion and narrowing confirmed this view. This case is of interest for two reasons: first, because of the uniqueness of the intussusception and, second, because of the spontaneous disappearance of the ureteral torsion as periureteritis subsided.

*Hemorrhage*—Hamer<sup>33</sup> reported a case in which fatal ureteral hemorrhage was caused by erosion into the iliac artery, the erosion occurring during drainage by indwelling catheter for pyelitis of pregnancy.

The patient was a woman 18 years old and five months pregnant. She had bilateral pyelonephritis, an elevated temperature and chills. Her condition was relieved by the insertion of ureteral catheters, which were left in place. The catheters were replaced three times in three weeks. On the day before the patient died, sudden hemorrhage caused her to lose a large amount of blood. In spite of performance of the usual necessary measures, the patient died. Postmortem examination

32 Bumpus, H. C., Jr. Intussusception of the Ureter, *Tr Am A Gen-Urin Surgeons* 32:127-131, 1939.

33 Hamer, H. G. Fatal Ureteral Hemorrhage Due to Erosion into the Iliac Artery. Report of a Case Occurring During Indwelling Catheter Drainage of Pyelitis of Pregnancy, *Tr Am A Genito-Urin Surgeons* 32:177-183, 1939.

showed the right ureter to be attached to the common iliac artery at the pelvic brim, and an opening 1 cm in diameter connected these structures at this point. The kidneys contained abscesses in the parenchyma and in the cortex. The right renal pelvis and ureter were full of blood clots.

This case was somewhat similar to those reported by Davidson and Taylor.

Hamer reported another case, in which a woman 31 years old and four months pregnant exhibited evidence of infection of the urinary tract. A ureteral catheter was inserted and was changed ten times during the following three months. The patient had marked anemia and received a number of transfusions of blood. Later she gave birth to a premature child and died. Necropsy showed that communication had existed between the external iliac artery and the right ureter.

The cause of the perforation in Hamer's case was fairly well established by the pathologist's report, yet there is reason for speculation as to the contributing cause, which may have been one of the following factors:

- 1 Use of too large and too rigid catheters
- 2 Repeated injury to the ureter in one situation as the result of numerous insertions of catheters
- 3 Pressure of the head of the fetus on the ureter containing the catheter so that the ureter was pressed against the vessel, the constant pulsation of which weakened the ureteral and vascular walls at the point of crossing

- 4 Changes in the ureteral wall incident to pregnancy

Paschkis, in the discussion of a case of perforation of the ureter by an impacted calculus, remarked that such an occurrence, although infrequent, is not extraordinarily rare. He questioned the supposition that the ureter ruptured at a site at which its wall was normal and expressed the opinion that manipulation during catheterization might have led to perforation in the particular case he was discussing.

*Dilatation*—Franché<sup>34</sup> called attention to a process which is the reverse of the well known repercussions of ureteral lesions on the renal pelvis and on the kidney, namely, an important influence of the pelvis and the kidney on the ureter, resulting in dilatation of the latter for which no adequate cause exists in the lower part of the urinary tract and which can be explained only on the basis of the existence of a pathologic condition of the kidney or of the renal pelvis, most commonly hydronephrosis or renal ptosis. Such dilatation may involve the entire

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34 Franché, O. Dilatation ureterale au cours des lésions pyélo-renaies, *J. urol.* 46:401-414 (Nov.) 1938.

ureter or may be localized in its upper two thirds, extending as far as its point of entrance into the lesser pelvis. The influence is not constant, however, and, although the dilatation may be considerably advanced, it does not necessarily affect the ureter, which may remain entirely normal in the presence of enormous hydronephrosis. There is no parallelism between the extent of the pyelorenal pathologic process and the degree of ureteral dilatation present.

It has been customary to believe that the changes under consideration are caused by pregnancy or that, at least, they have a genital origin. But the history of a woman who had never been pregnant and who had no history of involvement of the genitalia but who had a movable kidney would suggest that the cause lay in renal ptosis itself. Such an interpretation also seems to explain another fact that pregnancy has not explained, namely, the predominance of postgravidic sequelae on the right side, whereas it is well known that ureteropyelic dilatation during pregnancy is bilateral. It is known, however, that renal ptosis is more common on the right side in female patients, and this fact seems to throw some light on the cause of the ureteral dilatation under discussion. Additional confirmatory evidence is found in the fact that dilatation of this kind is found at times in men suffering from renal ptosis. A case was cited by Franche in which nephrectomy was about to be performed in some other surgeon's service, when Marion, being called in, advised that a pyelogram with the patient in the vertical position be made first, whereupon it was revealed that fixation of the kidney and not nephrectomy was needed. Nephropexy brought immediate relief, which had persisted for two years at the time of Franche's writing, the ureteropyelographic image at that time being perfectly normal. Two additional cases were described to show that such cases are not exceptional. Still other cases were presented, revealing that when the cause of ptosis or hydronephrosis has been removed ureteropyelic dilatation markedly diminishes and painful symptoms disappear.

In cases in which the condition might be considered "reversible," as has been explained, it would appear that the mechanism of production of ureteral dilatation can be nothing other than a state of ureteral atony, which in the course of time may result in permanent and definitive modification of the ureteral wall, a modification which in the earlier stages was transitory and reversible. It has been suggested that this atony is a reflex, possibly caused by irritation of a nerve center or of a neuromuscular center situated in the upper part of the ureter, where it might be produced by a kink, renal ptosis, the presence of an abnormal calculus or some similar anatomopathologic condition. In the present state of urologic knowledge this explanation seems the most plausible that can be reached.

Gloor<sup>35</sup> compared cases of megaloureter without obstruction of the urinary flow and cases of marked stenosis of the ureteral outlet in which only slight dilatation of the ureters is exhibited. He opposed the opinion that mechanical obstruction causes megaloureter and advocated Bard's theory that dilated structures similar to the ureter in the presence of megaloureter originate as a result of dysplastic changes in the walls of such structures. Gloor found no proof that inflammatory changes of the ureteral wall alone could cause large dilatation of the ureter.

#### PROSTATE

*General Considerations*—Wildbolz<sup>36</sup> discussed, in a paper read before the German Surgical Association, the treatment of benign hypertrophy and carcinoma of the prostate gland. The development of the normal prostate gland, the mechanism of prostatic hypertrophy and carcinoma of the prostate were discussed. He also reviewed and criticized the theory of hormonal influence. In another part of the paper, Wildbolz considered the operative and nonoperative methods of treatment: glandular therapy, operations on the genitalia (Steinach), high voltage roentgen therapy, suprapubic and perineal prostatectomy and transurethral prostatic resection. On the basis of Wildbolz' wide experience, he is especially able to discuss all these various methods of treatment. He expressed particular favor for perineal prostatectomy, which, he stated, is the only method which may produce a permanent cure of carcinoma of the prostate gland.

Kraas<sup>37</sup> reviewed results obtained in the various German surgical clinics in instances of transurethral resection of the prostate gland. He stated that there is a wide divergence of opinion as to the merits of transurethral resection and the open operation. He expressed the opinion that both methods have their place and that the operation should be suited to the particular condition of each patient.

*Hypertrophy*—Deming<sup>38</sup> stated that the early phases of benign prostatic overgrowth are found in the muscular walls of the posterior portion of the urethra in specimens observed at necropsy.

Benign prostatic overgrowth usually passes through two phases of development. The first phase is the development of a fibromuscular

35 Gloor, H. U. Ueber die Ursachen der Megaloureterbildung, Schweiz med Wchenschr. **69** 1080-1084 (Nov 4) 1939.

36 Wildbolz, H. Die Behandlung der Prostatahypertrophie und des Prostatacarzinoms, Zentralbl f Chir. **66** 770-782 (April 8) 1939.

37 Kraas, E. Prostatektomie—Prostataresektion Ztschr f Urol. **33** 553-559 1939.

38 Deming, C. L. The Development of Prostatic Hyperplasias, Surg, Gynec. & Obst. **70** 588-594 (Feb no 2A) 1940.

mass from the intramuscular stroma of the posterior part of the urethra. The second phase is invasion of the fibromuscular nodule by the epithelium of a prostatic duct. This epithelial proliferation develops prostatic glands and ducts of normal appearance.

The epithelial element overgrows the fibromuscular element so as to make the full-grown lesion appear glandular. The glands in the posterior part of the urethra and the prostate gland are not primarily involved.

The primary fibromuscular nodule resembles fibromyoma of the uterus and may be derived from a remnant of the musculature of the müllerian ducts.

Benign overgrowth of the prostate gland produces hyperplastic tissue and not hypertrophied tissue.

*Castration in Cases of Prostatic Hypertrophy*—Huggins and Stevens,<sup>39</sup> in discussing castration and benign prostatic hypertrophy, stated that in 50 cases of benign prostatic hypertrophy the prostatic epithelium varied from flat to tall cylindric, the latter type being found in every case.

From 3 men who had benign prostatic hypertrophy, specimens of prostatic tissue for biopsy were obtained at the time of castration and also twenty-nine, eighty-six and ninety-one days later. Epithelial atrophy was not present twenty-nine days after castration but appeared plainly at eighty-six and at ninety-one days after the operation. In 1 case there was a marked reduction in the size of the prostate gland at rectal examination and an increase in the size of the urinary stream within one month after castration. The evidence derived from castration concerning benign prostatic hypertrophy in man supports the view that the prostatic epithelium, at least, is under control of the testes.

*Total Perineal Prostatectomy*—Lowsley<sup>40</sup> stated that total perineal prostatectomy should be done more often than it is at present. It is indicated in cases of early carcinoma, chronic pyemia, intractable chronic fibrosis and calculosis and in certain cases of tuberculosis and adenoma of the prostate gland. He suggested that the membranous portion of the urethra be joined to the bladder with a mattress suture of ribbon gut, this procedure not only makes the urethra continuous with the bladder but plicates the external sphincter and prevents incontinence of urine. The success obtained in the cases in which the operation was done encouraged Lowsley to report the method in the hope that others would use it.

39 Huggins, C., and Stevens, R. A. The Effect of Castration on Benign Hypertrophy of the Prostate in Man, *J Urol* **43** 705-714 (May) 1940.

40 Lowsley, O. S. Total Perineal Prostatectomy, *J Urol* **43** 275-285 (Feb) 1940.

Vest<sup>41</sup> has introduced a modification of the conventional radical perineal prostatectomy of Young for carcinoma of the prostate gland. He said that this modification diminishes the liability to incontinence, which frequently follows the operation because of injury to the external urinary sphincter by the sutures used to approximate the margin of the bladder to the membranous portion of the urethra. In the performance of this anastomosis it becomes necessary at times to take sutures well through the triangular ligament, an action which must inevitably include and injure the external sphincter.

To avoid this, Vest, in uniting the bladder to the membranous portion of the urethra, has used three mattress sutures, which have been placed in the margin of the anterior part of the bladder, traverse the external sphincter on either side of the urethra just beneath the mucosa, continue just beneath the mucosa through the region of the sphincter through the triangular ligament and pass into the perineum just beneath the skin on the anterior margin of the perineal incision. When traction is made on these three sutures and when they are tied, a considerable part of the circumference of the cut margin of the bladder is drawn tightly against the membranous portion of the urethra and anchored there without any interference with or constriction of the sphincter in this region. The remainder of the bladder is then closed, and a figure-of-eight is used to complete the union of the bladder to the under margin of the membranous portion of the urethra.

Vest has used this modification in four operations, with satisfactory results.

*Transurethral Resection*—Tolson<sup>42</sup> reviewed the records of 356 patients operated on for relief of obstruction to the vesical outlet from 1924 to 1938, inclusive. One hundred and forty-four patients were operated on by means of modifications of the punch technic. During the period from 1932 to 1936, 96 patients were operated on by means of electrical resection. One hundred and sixteen patients were treated by suprapubic prostatectomy. For the entire period under discussion, the approximate ratio of resection to prostatectomy was 2 to 1. During 1938, resection was performed in 56 instances and prostatectomy in 4, a ratio of 14 to 1.

No patient less than 50 years of age was subjected to prostatectomy, whereas 6 patients less than 50 years of age underwent resection. In this group the obstruction was minor or moderate. Ten patients more than 80 years of age underwent resection. These patients had advanced degrees of prostatic enlargement.

41 Vest, S. A. Radical Perineal Prostatectomy. *Surg. Gynec. & Obst.* **70**: 935-937 (May) 1940.

42 Tolson, H. L. Prostatic Resection with Modifications of Young's Punch. *J. Urol.* **43**: 116-122 (Jan.) 1940.

The type of anesthesia employed for patients who underwent resection was low spinal anesthesia produced by procaine hydrochloride for 134, caudal anesthesia produced by procaine hydrochloride for 90 and local anesthesia produced by procaine hydrochloride for 16. Low spinal anesthesia induced by procaine hydrochloride is the anesthesia of choice the usual dose is 120 mg.

During 1938, 56 patients underwent resection. Forty-two patients underwent removal of less than 20 Gm. of tissue and 14 patients underwent removal of more than 20 Gm. of tissue. The maximal quantity removed at one operation was 69 Gm., the average quantity was 18.1 Gm.

Twelve patients in whose cases preoperative diagnosis of prostatic carcinoma had been made underwent resection. In these instances there was obstruction to urination which demanded relief. The patients were treated postoperatively by high voltage roentgen therapy.

Patients who underwent resection by cold sharp steel experienced fewer complications than did patients who underwent resection by the electrical method. The problem of infection is less annoying, and the period in which pyuria is present is shorter, when the former technic is employed. Prolonged pyuria and prostatitis occurred in a large percentage of the patients who underwent electrical resection and infrequently in those who underwent cold resection. Prostatitis following cold resection responded more promptly to treatment.

Extravasation of urine occurred in 2 patients, but it was immediately recognized and treated by suprapubic drainage. Overdistention of the bladder with irrigating fluid was the probable cause of this complication. For some time it has been Tolson's custom not to drape the lower portion of the abdomen, this permits his assistant to note the degree of distention of the bladder.

Epididymitis occurred in 5 patients who had not undergone vasectomy. Vasectomy has been used for the majority of patients who undergo resection, and in no instance has epididymitis occurred after vasectomy. A considerable number of patients have objected to being sterilized. Two patients treated by resection, aged 69 and 72 years, subsequently became fathers of additional members of their families.

Ten deaths (4.1 per cent) occurred in the group of 240 patients treated by transurethral resection. In the group of 116 patients treated by suprapubic enucleation there were 9 deaths (7.7 per cent).

Removal of the obstructing portion of the prostate gland by sharp cold steel, with coagulation of only the bleeding points, is accompanied by minimal injury to the residual portion of the prostate gland. Early epithelization of the prostatic portion of the urethra is rendered possible by the presence of a freshly cut surface composed, except for the slightly coagulated points, of living cells. Consequently, convalescence is relatively short, and there is minimal morbidity.



Foley<sup>43</sup> stated that the status of the surgeon who does transurethral resection determines the status of prostatic resection in his hands but not in general. Great competence of such a surgeon makes prostatic resection a valuable procedure to be used extensively, the asserted upper limits of the procedure's utility being 80 to 95 per cent of cases. Limited competence of the surgeon makes prostatic resection a procedure of limited value and restricted use, the asserted extent of its successful use in the hands of such surgeons is 15 to 50 per cent. For the completely incompetent urologic surgeon who uses the procedure, no gland is small enough and no transurethral operation is sufficiently foolproof to make resection the operation of choice. In such hands, if the surgeon possesses any surgical ability whatever, open operation is the operation of choice. Skill, ability and experience on the part of the surgeon who does transurethral resection extend the limit set by the size of the gland and the limit of technical difficulty within which resection is the operation of choice.

Suprapubic and perineal prostatectomy are the same perfected and useful operations that they were before any one ever heard of resection. They yield nearly perfect results, with a low mortality rate. Neither of them makes anything like the demand made by resection on special talent, long training in cystoscopy and experience with the procedure itself.

The process of development and perfection of suprapubic and perineal prostatectomy entailed poor results and a mortality rate that now seems shocking. There was no alternative. Perfected technic, modern surgeons well skilled in the procedure of open prostatectomy and what they contribute to human welfare have vindicated the effort. The process of development of transurethral prostatic resection to its present stage of perfection likewise entailed poor results and a mortality rate that now seem shocking. Fortunately, reversion to major prostatectomy was not the only alternative for all urologic surgeons who did transurethral resection. A perfected technic of resection and urologists who are skilled in the procedure of resection now vindicate the effort, and it remains only for the urologic surgeon who uses transurethral resection to determine his status.

The surgeon who continues routinely to use either suprapubic or perineal prostatectomy on the ground that in his hands it is the operation of choice and that in his hands it best serves the welfare of the patients is fair to the patient, to medical science and to himself.

Urologists and general surgeons alike must limit their use of resection according to their ability to perform transurethral resection, and

43 Foley F E B. The Present Status of Transurethral Resectionists, Competent and Otherwise. *J Urol* 43: 565-571 (April) 1940.

they must always employ the operation that best serves the welfare of the patient in their hands, whether it be by the suprapubic the perineal or the transurethral method. It is desirable to be able to use each procedure with skill, ability and reasonable competence, but shortcomings in respect to any of the three procedures are no reflection on that procedure, nor do they enhance the value of the others. If this is recognized and if surgeons are governed accordingly, prostatic operations will be perfectly individualized in respect to both the patient and the surgeon, and urologic surgeons will best serve the welfare of their patients.

*Carcinoma*—Silverstone<sup>44</sup> stated that radium has a definite place in the treatment of carcinoma of the prostate gland. To be of maximal benefit, irradiation should be uniform, and, since massive local destruction is to be avoided, multiple foci of low intensity should be used. Perineal exposure of the prostate gland allows a uniform distribution of needles, without concentration of the dose at any mucosal site. Neoplastic extension in the neighborhood of the seminal vesicles can also be dealt with, if marked sepsis or renal inefficiency is present, such extension must be dealt with by preliminary drainage, either by indwelling catheter or by suprapubic cystostomy.

Radium is not universally applicable. The patient who has distant metastases and pain referred to the lower limbs, usually caused by glandular metastases in the pelvis, will be better without treatment by radium. About a third of patients have demonstrable metastases when they are first seen. If the general condition is poor or if the kidneys are inefficient, radium should not be used unless and until improvement takes place. When marked obstruction is present, conservative surgical intervention usually should be carried out in addition to radium therapy. Patients treated with radium should be followed up carefully, since if fibrosis occurs dilation or endourethral resection may be necessary.

For treatment to be of value in cases of carcinoma of the prostate gland the condition must be diagnosed earlier than is usually the case. It would seem that this can be accomplished only by the routine rectal examination twice a year of persons more than 50 years old. Such examination may reveal areas of induration, the pathologic aspects of which can be confirmed by resort to aspiration of material for biopsy.

*Sarcoma*—Stevens and Barringer<sup>45</sup> presented a paper concerning sarcoma of the prostate gland and anaplastic carcinoma. The latter is

44 Silverstone, M. Radium in Treatment of Carcinoma of the Prostate, *Brit J Surg* 27 498-505 (Jan) 1940

45 Stevens, A. R., and Barringer, B. S. Sarcoma of the Prostate. *Tr Am A Genito-Urin Surgeons* 32 275-303, 1939

readily and commonly confused with sarcoma. The purpose of the paper was to correlate existing facts and thus perhaps to clarify ideas concerning these diseases.

Brief histories were appended of 16 patients who had prostatic neoplasms. Five of the tumors were proved microscopically to be myosarcomas, 1 to be lymphosarcoma and 1 to be spindle cell sarcoma. There were 3 carcinomas in young men, for the last 6 patients a clinical diagnosis only of malignant disease had been made, the lesion being called sarcoma. It is of interest to note that 4 of these patients were subjected to operation for prostatic abscess. According to the literature, only in rare cases can sarcoma of the prostate gland be controlled for more than a few years by present methods. On the basis of a review of the histories, the records are discouraging. The diagnosis is usually made late in the course of the disease, and the course is rapidly downward, with occasional temporary regression of the tumors if the patient is subjected to roentgen therapy.

The tissue giving origin to the tumor forms the basis for perhaps the simplest and most satisfactory pathologic classification of prostatic neoplasms. Stevens and Barringer, therefore, suggested that sarcomas of the prostate gland be segregated in three groups:

- 1 Leiomyosarcoma and rhabdomyosarcoma, which take origin in the musculature of the prostate gland. These two tumors are much alike in growth and clinical manifestations.

- 2 Lymphosarcoma, which originates in the lymphatic tissue of the prostate gland. This tumor formerly was a disputed entity but is now generally recognized.

- 3 Sarcoma, which has an undetermined origin. The term includes spindle cell sarcoma, fibrosarcoma, myxosarcoma, round cell sarcoma and giant cell sarcoma.

For clinical reasons, Stevens and Barringer added to the aforementioned groups a fourth lesion, which is not sarcoma but anaplastic carcinoma. It has various features which resemble those of sarcoma and is often mistaken microscopically for lymphosarcoma.

Metastasis from carcinoma of the prostate gland takes place usually through the lymphatic channels but may progress by means of the blood vessels. It is probable that the metastasis to bone occurring in this disease may take place by either the lymphatics or the blood vessels. The picture is reversed in cases of sarcoma of the prostate gland, in which the usual routes of metastasis are the blood vessels. Lymphatic metastases from prostatic sarcoma are not rare, however.

The less malignant sarcomas often cannot be distinguished from non-malignant hypertrophy of the prostate gland. When the diagnosis is made on the basis of the specimen removed, any future treatment depends on the pathologist's opinion and the subsequent course of the disease. The more malignant tumors, whether they are lymphosarcomas, myosarcomas, sarcomas of undetermined origin or anaplastic carcinomas, generally produce one or more indications that an unusual neoplasm is present. These indications are: The patient is below the age at which prostatic hypertrophy or prostatic carcinoma might be expected to appear, he gives a short history of the development of the lesion or his discomfort, the prostate gland is of great size, the neoplasm often almost fills the rectal lumen, the neoplasm is elastic and irregular as contrasted to the irregular indurations of prostatic carcinoma, a suprapubic tumor is present which is continuous with the prostatic tumor, generalized lymphadenopathy is present, and the patient has experienced rapid loss of weight and cachexia, although the two symptoms last mentioned generally are absent.

Prostatic abscess, prostatic carcinoma, tumor of the bladder, extravescical tumor, cyst of the prostate gland and massive stone of the prostate gland are all conditions which may be mistaken for prostatic sarcoma.

Stevens and Barringer's experience and the literature both demonstrate the superior value of irradiation over surgical procedures in the treatment of this condition.

*Leiomyoma*—Deming<sup>46</sup> discussed the significance of leiomyomas of the prostate gland. "Leiomyoma" is a term loosely applied to tumors of smooth muscle and connective tissue. Deming found in the literature 32 cases of leiomyoma of the prostate which were available for study. The condition of the youngest patient, who was 24 years of age, was described in a case reported by Koening in 1936, the condition of the oldest patient, who was 80 years of age, was described by Patch and Rhea in 1935. The average age is 61.7 years.

The cases are sharply divided into two groups. Cases in which the patients had obstruction of the neck of the bladder simulate in every way those cases, familiar to urologists, which are described as cases of "prostatism." Reports of necropsy showed that obstruction of the neck of the bladder, infection of the urinary tract, distention of the bladder and dilatation of the ureters and renal pelves were present, and in this particular group there was a majority of 27 cases. The average age of the patients was 64.7 years, approximately the same as that

<sup>46</sup> Deming, C. L. The Significance of Leiomyomata of the Prostate. *Tr. Am. A. Genito-Urin. Surgeons* **32**: 263-273, 1939.

for patients with prostatic hypertrophy. The second group of patients had rectal symptoms without urinary symptoms. Rectal examination showed a smooth, elastic enlargement of the prostate gland. There were 5 patients in this group, and the average age was 45.2 years.

In the series of 32 cases, 5 patients died without undergoing operation on the prostate gland. Twenty patients were operated on by the suprapubic route. The youngest patient, 24 years of age, who had no urinary symptoms, was included in this operative group. All the patients recovered. Six were treated by perineal enucleation of the tumor. Five recovered, 1 died within twenty-four hours, of shock. Transurethral resection was performed in only 1 case, it was successful. Twenty-six of the 27 patients on whom operations were performed recovered, the operative mortality rate being 3.7 per cent, which approximates the results of prostatic operations in the best clinics.

The tumors varied in size from 5 to 570 Gm., they occupied the urethral portion of the prostate gland.

Many authors have described leiomyomas as encapsulated tumors of smooth muscle, simulating myomas of the uterus. In other reports, leiomyomas have been described as nonencapsulated tumors of smooth muscle with interlacing fibers having a whorled appearance.

Up to the present, the diagnosis of leiomyoma of the prostate gland has not been made preoperatively. Rectal palpation does not distinguish leiomyomatous and glandular tumors. It is possible that the occurrence of rectal symptoms in young men might suggest the existence of such a neoplasm. Cystoscopically, leiomyomatous enlargements of the prostate gland are similar to the glandular masses in situation, size and character. A specimen for biopsy obtained by the transurethral method provides a means of diagnosis. This method was employed in only 1 reported case, but the lesion was not diagnosed until microscopic study had been made.

*Abscess*—Schwartz<sup>47</sup> found, in studying the problem of prostatic abscess and nonsuppurative prostatitis, that the nonspecific hematogenous type of abscess is as common as that caused by the gonococcus. Of the 12 cases of nonspecific abscess reported, there was sufficient clinical evidence in 4 to warrant the designation of "metastatic" or "embolic" abscess of the prostate gland. The history of several of the other patients suggested that the abscess was secondary to a focus elsewhere, which had already subsided when the patient presented himself. It is justifiable to assume that metastatic abscess of the prostate gland occurs much more often than is generally appreciated.

<sup>47</sup> Schwartz, J. Metastatic Abscess of the Prostate Gland. *J. Urol.* **43**: 108 (Jan.) 1940.

Prostatic abscess is not a serious lesion if it can be recognized in time and if it can be properly treated. A conservative policy is justifiable and is often of great value, but surgical drainage is imperative when there are unmistakable signs of a prostatic abscess which does not respond to reasonable nonsurgical measures. Recovery of the patient after surgical drainage is usually more prompt than when drainage has not been instituted.

*(To Be Concluded)*

## Notices

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### SPECIAL FEATURES FOR COMING YEAR

It is proposed to continue the publication of symposiums during the coming year and, in addition, to publish review articles which will cover the advances in all fields of surgery. The first of these articles will be by Drs Alton Ochsner and Michael DeBakey, it will be entitled "Carcinoma of the Lung" and will appear in an early issue. A paper by Drs W H Cleveland and Waltman Walters, "Surgical Lesions of the Pancreas. A Review," will appear shortly thereafter. Other members of the Editorial Board will sponsor articles of this type, and the board feels that in this way the recent developments in all fields of surgery will be brought to the attention of the readers of the ARCHIVES.





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## SOME OF THE MEDICAL CENTERS OF SOUTH AMERICA

G GREY TURNER, LL.D., D.Ch., M.S., F.R.C.S.,  
F.A.C.S., F.R.A.C.S.  
LONDON, ENGLAND

### Foreword

In the Jan 13, 1940 issue of *The Lancet* (London, England) Prof Grey Turner published a most interesting account of his visit to some of the medical centers in South America. The article describes the excellent work being done by South American Surgeons, and for this reason as well as because it would prove of great value to North American surgeons contemplating a visit to South American clinics, the chairman of the Editorial Board asked Professor Turner to prepare a similar article on the same subject for publication in the ARCHIVES. Professor Turner graciously complied, and his contribution, part of it taken from *The Lancet*, follows

These brief notes are the record of a visit, made in company with my wife, to Buenos Aires, Argentina, and other South American republics and cities during September 1939 under the aegis of the British Council for the Promotion of Cultural Relationships. The voyage from England, with calls in Portugal, Madeira and Brazil, was in every way delightful, though the last few days were darkened, in more senses than one, by the threat of war.

When we arrived at Montevideo, the principal city of Uruguay, after sailing for several days under wartime conditions, it was delightful to be greeted by H. B. M. Minister Mr. Millington-Drake and by the surgeons of the city, who had most thoughtfully arranged a deputation to welcome us. A further surprise was in store, for we were soon joined by Dr. Oscar Ivanissevich and Dr. Castro O'Connor, who throughout proved such an admirable and efficient secretary and who came on behalf of the faculty of medicine of the University of Buenos Aires to offer us a further welcome and to chaperone us during the concluding stages of our journey up the river Plate. When we landed at our destination, Prof. Jose Arce (fig 1) and several others were waiting with a further warm welcome, and from that moment until we left, nearly two weeks later, we met with the greatest kindness, and a handsome motor car was always at our disposal.

My mission was to deliver a series of lectures, to make contacts in professional and academic circles and to see as much as time would

permit of the work of the hospitals and ancillary institutions. Incidentally, these activities were interspersed with numerous social functions, lavish hospitality being shown on every side.

Buenos Aires ranks high in the scale of great cities, not only because of its size but because of its fine layout and notable architectural features. It was a surprise to find such a city with between two and three million inhabitants, for, though it is over 6,000 miles from the shores



Fig 1—Prof Jose Arce, director of the Institute of Clinical Surgery of Buenos Aires

of Great Britain, it is a sort of mixture of London, Paris and New York. There are wide open spaces, many public gardens and no end of fine statues. Much land along the river bank is being reclaimed and laid out as public parks with broad boulevards and flower borders, and every scrap of spare ground seems to be looked after, even though at some not very distant date it may be destined to be built on. The whole town breathes a fine civic spirit, which indeed seemed to be general in most of the South American republics which we visited. The numerous hospitals are for the most part old buildings in the Spanish

style, with patios, colonnades and ample open spaces, laid out with flower beds and shrubs between the pavilions. But in most cases new blocks are springing up in the grounds of the original institutions, and, quite apart from new buildings, alterations have been made to bring the various departments up to date. Fortunately, as yet nothing has been done to overshadow the original style, which reminds one so much of the old days of Spanish domination. Inside these old hospitals, what struck one more than anything else was the way that every hole and corner had been put to some useful purpose. It was remarkable to find parts of the corridors, window recesses and odd corners converted to some useful purpose, apparently without regard to a build-

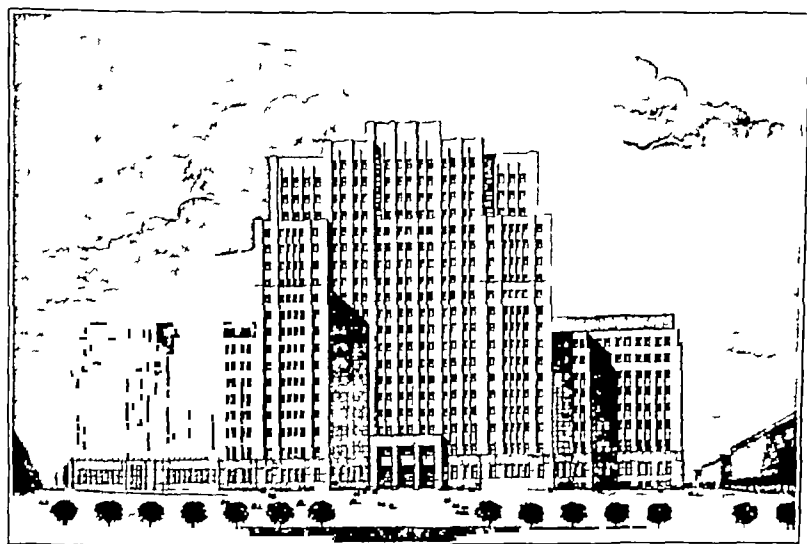


Fig 2—Model of the new Institute of Clinical Surgery in the course of erection in Buenos Aires

ing scheme but simply that the new-found space might serve the end in view without delay. The use of light tiles and light paint converts dark corners into bright spaces, and of course the plentitude of marble and of sunshine is a great help. But the days of some of the old hospitals seem to be numbered, and just opposite the Institute of Clinical Surgery a large modern building which is springing up will form a hospital center and medical school on the American plan (figs 2 and 4). The central part is to be eighteen stories high, and, as the illustrations show, the other parts are in keeping. Many of the clinics as they are today remind one of the Continental style and are more of the French than of the Nordic pattern, and the caps and aprons worn by the professors and their staff are very reminiscent of Parisian days. In the well appointed clinic of Prof Jose Arce the influence of that

master of organization and fount of inspiration was obvious on every hand. There seemed to be no shortage of competent assistants, and it would appear that the idea of sticking to the parent hospital attaches a great many of the senior men to the various posts and probably means that there are always lots of well trained men willing and anxious to continue at hospital work in the hope of attaining preferment. But the atmosphere was good, and the clinic seemed to claim the attach-

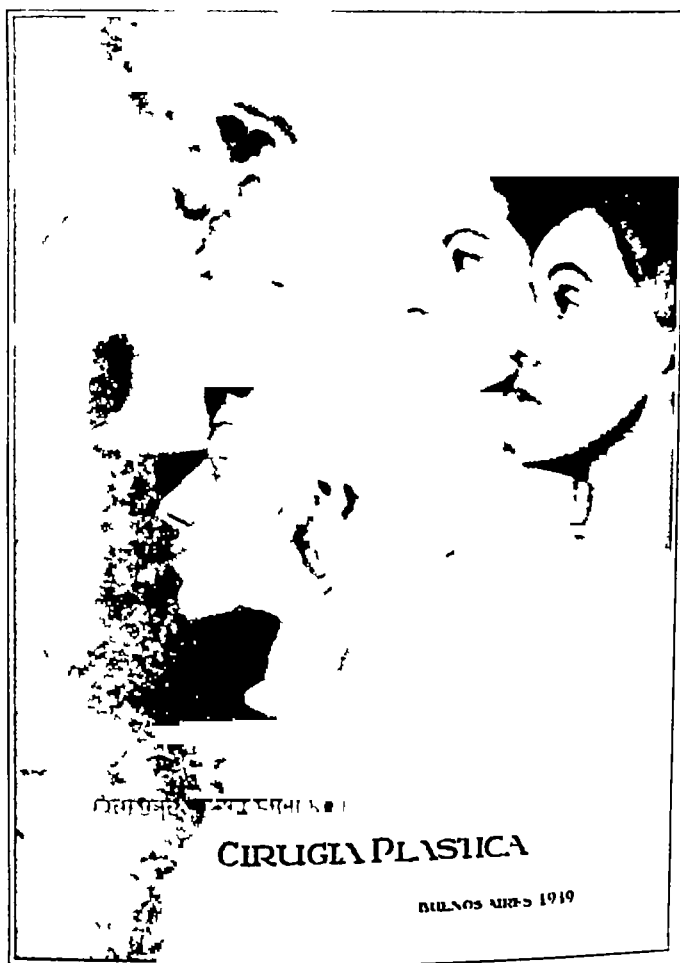


Fig 3—Cover of the catalog of the exhibition of plastic surgery

ment of everybody about it. A good deal of the teaching is done in rather an old-fashioned amphitheatre, which is also used for operations, but the tutorial work is conducted in smaller classes in the wards. At operations one notices the frequent use of local and spinal anesthesia, but it was explained that this was largely due to the disinclination of the Argentino to lose consciousness, it is a wide awake country, and the patients like to know what is going on! But general anesthesia is gaining a foothold, one saw some of the latest machines in occasional use, and at least one member of the medical profession is devoting

himself entirely to work as a specialist in anesthetics. The operating lists are singularly like those at home except that, of course, the surgical management of hydatid diseases still takes a prominent place, though we were told that the disease is not nearly so frequent as in the immediate past. Surgery of the lung is coming into its own, and it was interesting to find that neurosurgery is mostly in the safe hands of a Harvey Cushing pupil and disciple. In the clinic of Arce, plastic surgery has been largely developed by Dr. Oscar Ivanissevich, and just at the time of my visit an exhibition of photographs, diagrams and models (fig 3) dealing with plastic surgery and its results was being held in an empty ward, which in ordinary times would accommodate some 25 or 30 patients. Nearly all the photographs were in color and were illuminated from behind, and they made a very fine show. The municipal art gallery had loaned some oil paintings of appropriate nudity, and these helped to enliven the more technical exhibits. The exhibition was arranged to commemorate the twenty-fifth anniversary of Professor Arce's occupation of the chair of surgery in the university and to express the warm feelings of his pupils for the stimulating example of their maestro. The inauguration ceremony was attended by representatives from other towns in the Argentine and from the neighboring republic of Uruguay. On that occasion I was glad to be given the opportunity of saying something about the general principles involved in this branch of surgery.

The medical clinic of Professor Mariano Castex is a very active unit, and there were numbers of enthusiastic assistants, all most anxious to exhibit their work. As in other departments, I was struck with the way small spaces and odd corners had been used to accommodate laboratories, examination rooms, secretarial offices, etc. One small ward was devoted entirely to diseases of the peripheral vascular system, and there I saw numbers of elderly men with advanced vascular starvation, in some cases with impending loss of the toes or part of a foot as the result of gangrene. Professor Castex explained that they made a special study of these conditions and that by various means, but especially by use of subcutaneous injections of carbon dioxide, they were getting very good results, in fact, during the previous two years it had not been necessary to do a single formal amputation of a limb, although some patients had lost a small part of the foot. In nearly every case recovery was complete enough to allow the patient to resume his previous occupation. There was ample evidence of activity in other branches of medical work, such as the treatment of carcinoma of the bronchus and lung (which they find to be very common), bronchiectasis and nephritis and the geographic distribution of renal calculi, etc. Each clinic seems to have its own roentgen department, and the results shown me were very good indeed.

At the Rawson Hospital, with its new department of surgery, I saw Prof Enrique Finochietto, who is doing some very nice work. Before operating the professor demonstrated the steps by a series of excellent colored drawings which he had himself prepared. These were exhibited on an easel in the theater, being turned over one by one, they provided a most effective guide to the work proposed. Finochietto's technic for gastrectomy by the Billroth no 1 method is well known and largely used in South America, and it was a treat to see it completed by such a master. The local anesthesia was perfect. I noticed that Duval's lung forceps was largely used and was certainly a most effective handle for the viscera. Some remarkable and curious esophageal conditions had been collected for my inspection. Many of the patients come from the campo, that is, the region of enormous open plains which forms so much of the country of the Argentine. The agricultural workers there do not seem to bother much about their physical complaints until they are most obvious, which probably accounts for the extremely advanced state of many of the pathologic conditions which Professor Finochietto's assistants were able to demonstrate. At the Hospital Ramos Mejia I met Dr A. Ceballos, a recent visitor to Great Britain and an enthusiastic worker. The theater there is of the ultramodern type, any but the most intimate visitors are entirely excluded from the floor and find places in a gallery which is really outside the room and from which they look down on the operations through plate glass screens, communication being established through the medium of loudspeakers. Though probably not contemplated, it was not surprising to look up and see visitors whiling away the tedium of looking at some complicated proceeding from this considerable distance while enjoying a cigaret. Dr Ceballos demonstrated the case of a young boy on whom he had recently carried out a total pneumonectomy, with an excellent result. A visit to the wards showed a new type of construction, with which I was entirely unfamiliar. Inside the long ward there were built partitions extending about 6 feet (1.8 meters) high and surrounding a space large enough to accommodate two beds, which as a rule faced the window. In a long ward this arrangement provides a certain amount of privacy, but it occurred to me that it is probably rather trying for the patients, especially when the sky and the sun are both bright. In the same hospital on another day I met Dr Robertson Lavalle, whose work on the treatment of tuberculosis of bone has been the subject of discussion for some years. I feel that I cannot usefully comment on his methods, but I was shown 1 or 2 patients with evidence of well developed Pott's disease who had been treated by his technic of bone puncture and who were apparently completely cured, though no fixation by plaster or apparatus of any sort had been employed and no long period spent in bed. Dr

Lavalle operated on a typical Pott's spine. A bone fragment about 2 inches (5 cm) long and about  $\frac{1}{4}$  inch (0.6 cm) thick was cut from the front of the tibia, one side of the spine near the disease was then exposed by an incision about  $3\frac{1}{2}$  inches (8.8 cm) long, as in the first stage of laminectomy. A hole was then made with an instrument like a bradawl from the root of the lamina obliquely forward into the vertebral body just above the main lesion. Into this hole the spigot of tibial bone was driven, and the incision was closed. As soon as the wound had healed the patient was to be allowed to get about freely, without retentive apparatus of any sort. I also saw illustrations and roentgenograms of cured lesions which left one bewildered and wondering. This subject was constantly discussed in the Argentine, and Dr. Lavalle and his disciples seemed to be satisfied about the efficiency of the plan. I could not help feeling that there must be something in this method, and yet what that something is or what is the dividing line between success and failure I am unable to surmise.

At the Hospital Rivadavia, with Dr. A. J. Bengolea, I saw some excellent results in cases of intractable vesicovaginal fistulas following labor, treated by transplantation of the ureters. I also saw many specimens of large gallstones which had passed spontaneously without operation as a result of administration of magnesium sulfate through a duodenal tube. Dr. Bengolea is investigating problems of biliary surgery, for his activities in the field of gynecology and the realm of general surgery seem to be interchangeable. With a British colony of over 50,000, it is not surprising that the British hospital in Buenos Aires is the largest outside the British Isles, and it was nice to find that half of the new hospital with its fine wards and spacious balconies was already completed. The staff, who are all of British origin, are keen and enthusiastic. The buildings of the medical school are delightfully spacious, reminding one of those of the Medical Faculty in the University of Saragossa in Spain. My visit was made in the evening, and in the absence of sun the buildings appeared gloomy. It was very difficult to realize that the enormous lecture theater, after the style of those one sees depicted on the title pages of some of the old folio works on anatomy, was only about a hundred years old. The carved scroll on a canopy above the lecturer's platform was a fine piece of work, which did not seem to be appreciated, though the comfortable seats covered with plush must have been somewhat of an attraction. The days of this particular theater are numbered, for it is to be replaced by a modern theater or series of theaters in the new building which is rapidly rising from the ground in the vicinity (fig. 4). It was easy to lecture to the enthusiastic audience which collected, but one soon realized that punctuality had not become a reflex among professional circles in the Argentine. I spoke in English, using lantern slides and films, and was assured that the great majority of those present under-

stood me quite well, as English is commonly spoken and is at least understood by those in academic circles in Buenos Aires. For the lecturer who must perforce employ English in a foreign country the secret is to talk slowly and distinctly, remembering that it sometimes makes for clarity to take time to give an alternative rendering of some word or phrase. An odd word or two of Spanish or French here and there may dispel an obscurity in a surprising way. In the provincial towns and in Chile the gist of what I said was translated as I went along, but good slides and films with some captions in Spanish went a long way to make up for linguistic deficiencies. The audiences were most attentive and did not appear to mind rather long sessions.

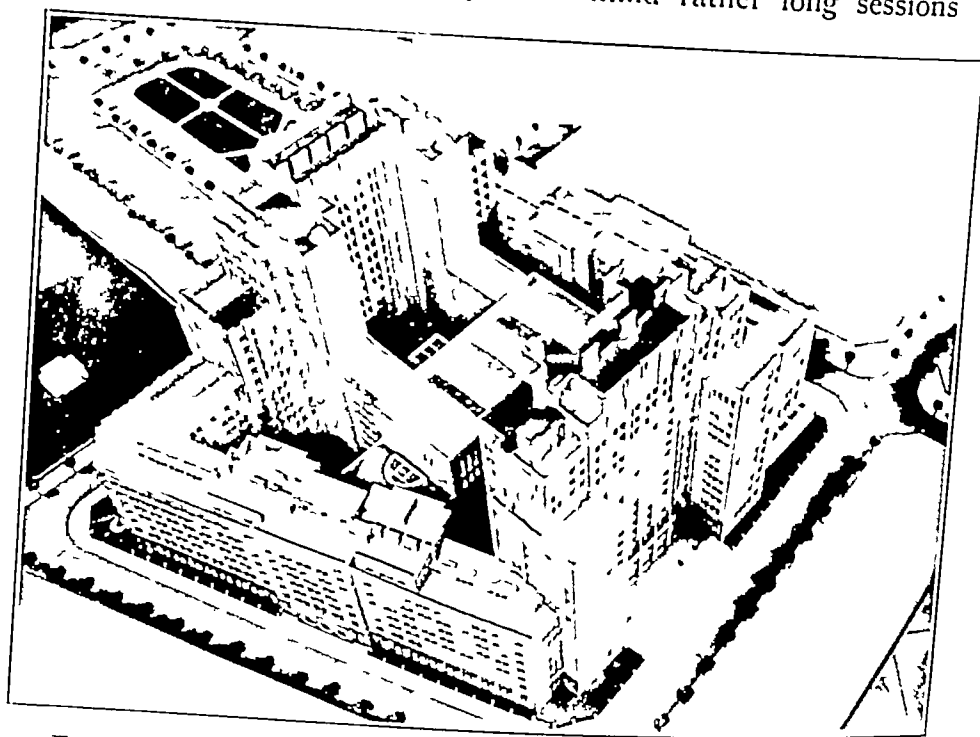


Fig 4—Model of the Institute of Clinical Surgery, seen from above

It was interesting to learn that the medical course in the Argentine is practically free and that the students have some word in the choice of their professors. The exercise of this privilege accounted for a rather noisy meeting which the students were holding in one of the corridors just outside a lecture theater and for an exhortation chalked in big letters on a wall in the school, urging the claims of one teacher rather than another!

The morgue is not usually a very attractive feature of any city, but that certainly does not apply to Buenos Aires, for I do not hesitate to say that it was one of the most interesting places in connection with medicine which it has ever been my privilege to visit. The director has a highly developed artistic sense and a stimulating personality, and



this accounts for the way the building is embellished with marble, stained glass windows and decorated iron work and is further adorned with pictures and statues. There are growing plants, flowers, trickling water and soft lights, and it only requires the enchantment of music and incense to make one think of some scene from the Arabian Nights. The office of the director was much more like the bureau in some great art collection than the administrative office of a dead house. The whole idea is to soften the poignancy of death without destroying its mystery. The institute reflects great credit on everybody concerned, for all the necessary work has been done on the premises. The modeler who makes the death masks was responsible for the statues, another of the staff painted the pictures, the engineer who looked after the refrigerator plant made the decorated iron work, and so on. The post-mortem room itself was beautifully clean and was so effectively air conditioned as to be entirely free from smell.

One of the best features is a museum of medical jurisprudence which would have delighted our British medical jurists. The director apologized for its small size, but it is about as large as the war collection at our College of Surgeons Museum in London and appears ample. There is housed a wonderful series of actual specimens illustrating all kinds of wounds and other injuries, burns of all degrees up to complete charring of the body, lightning injuries, the effects of poisoning by chemicals and gases and the conditions causing sudden death. All kinds of crimes were depicted "in the flesh," and some were so realistic as to be revolting. The specimens are beautifully preserved and exhibited, and where necessary there are also wax models, diagrams and photographs. Each exhibit has a full descriptive label, and copies of the complete notes on every specimen are kept in the museum and are readily available. The morgue is, of course, intended for the most part for the reception of bodies sent by the police, but I understand that by request any postmortem examination can be conducted there. The dossier of every subject is complete, and in one folder are all the particulars furnished by the police and the relatives. When available there are copies of the clinical notes, complete lists of the possessions found on the body, careful records of the examination made, records of chemical tests, photographs of the body, newspaper cuttings, letters and, in fact, everything relevant, preserved and kept together. All is most complete and is carefully dated and always readily available. It was an unexpected experience, after an hour or two spent in the building, to be invited to the director's office and to have the opportunity of talking over pathologic experiences seated in comfortable chairs in artistic surroundings and regaled with delicious coffee and cigarets.

A visit to the Institute of Experimental Medicine, which is directed by Prof Angel Roffo (fig 5), proved most interesting. This is on the outskirts of the city, where it occupies a very large area (fig 6). The many pavilions are situated in grounds which are artistically laid out. The name does not quite give the proper impression of the activities of the work carried on here, for large numbers of patients are seen and treated, and the institute deals with problems which arise on the clinical side as well as with experimental and laboratory work. The hospital part contains not only the large outpatient department but wards for



Fig 5—Prof Angelo Roffo with his visitors (September 1939). From left to right, the photograph shows Professor Roffo, Mrs Grey Turner, Professor Turner and Dr Castro O'Connor.

resident patients, laboratories, operating theaters and ample provision for treatment by irradiation and all the ancillary methods which may be necessary in cases of malignant disease. The equipment for high voltage roentgen therapy appeared to be complete and adequate, and at the time of my visit they were engaged in installing some newer and very high voltage machines. The professor was hopeful that he had overcome the difficulty about wastage of the tubes as a result of the development of a method of cooling by oil. It was instructive to talk over the results which had so far been obtained. No extravagant claims were made, but

one could judge from the records that the work was done extremely carefully and systematically and that probably the best results obtainable were being secured. To enhance the value of the records extensive use is made of pictorial methods, and in all cases photographs are made not only at the commencement of treatment but repeatedly throughout its course. We heard of remarkable results in some few individual cases, but these one almost comes to expect in cancer clinics, and it is difficult to avoid the conclusion that many of them are in the nature of freak results which are unlikely to be repeated even by employment of exactly the same methods in comparable cases. So far they have had little success in the treatment of malignant disease of the esophagus or of intra-abdominal disease, and the professor appeared to be quite hopeless about the outlook for malignant melanoma. For cancer of the rectum operation is largely employed, but irradiation is used as an adjunct, and

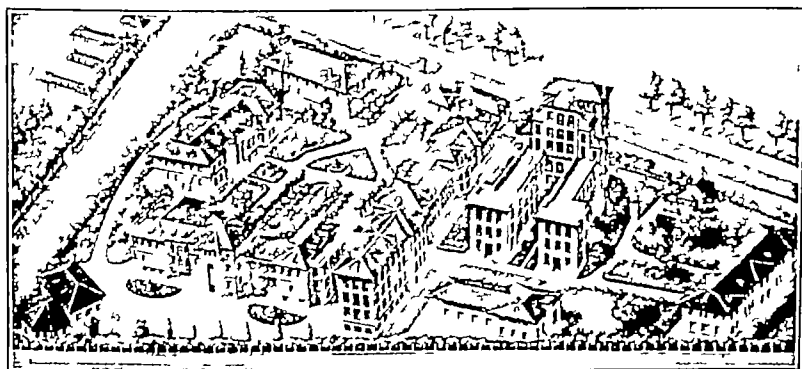


Fig 6—Institute of Experimental Medicine in Buenos Aires

so it is with cancer of the breast and cancer in other situations. I got the impression that close study of the methods would prove of great interest and value. As in all other countries that enjoy a maximum of sunshine, cancers of the skin are very common, and here they can claim a large proportion of excellent results by irradiation, with a minimum of deformity. The professor has been very interested in the problems connected with this particular type of disease, and by examination of the skin by a special lamp he is able to detect those cases in which heavy deposits of cholesterol suggest a tendency to development of malignancy. All the work is checked, and the colored figures of the cutaneous lesions were very convincing. In the institute there is a pathologic museum devoted to malignant disease in all its varieties. In the laboratories they are at the moment particularly interested in the part that tobacco may play as a carcinogenic agent. Quantities of tobacco of all varieties were being investigated, and in every case they had extracted a thick, black,

oily-looking substance which contained the carcinogenic agent in varying proportions, we saw many experimental animals in which various types of surface cancer had been produced by painting with the product

After this demonstration one could appreciate the idea behind propaganda posters which showed what was supposed to be the carcinogenic agent falling from a cigaret and depicted as flowing like a great black cloud over the greater part of the cancer-ridden globe. A similar substance can be extracted from soot particles from the air. It was quite alarming to see the large quantity of soot which had been collected in one of the filters, though one would have thought that the institute was situated in a particularly soot-free part of a not very sooty city. They have a remarkable collection of tissue cultures which had been going on for a long time, and the study of various problems by this method seems to play an important part in their work.

The record and literary department appears to be complete, for they endeavor to cover the world literature dealing with cancer. The huge pile of reprints from the daily post bag looked most formidable, and we saw a couple of clerks at work going through the articles and making epitomes, which were filed in a card index system, but I wondered if this system were sufficiently personal to be as useful as the labor involved would lead one to expect.

A few hours is far too short a time to spend in this institute, and the interested visitor ought to have two or three days at his disposal to get the most value out of such a visit.

I must just mention the house of the Argentine Medical Society, which occupies something of the same position in the medical community as does the Royal Society of Medicine in London. In addition, it is affiliated with the societies of outlying towns, and it also extends hospitality to other medical societies, which hold their meetings in its fine premises. They have nice lecture rooms, reading rooms, committee rooms and a very good library and are anxious to establish closer connection with the similar institutions in our own country. Dr Carlos Mainini is the president, and I was told that the flourishing condition of the institute was entirely due to his enthusiasm, his capacity for organization and the tact and industry which he has applied to its development.

No account of Buenos Aires, however brief, should omit some mention of the truly marvelous collection of prehistoric animals preserved in the museum at La Plata, which is just thirty-five miles from the capital.

From Buenos Aires we went down to Montevideo, which is the capital of the Republic of Uruguay. This attractive city is 123 miles by river boat from Buenos Aires, the journey being made over night. The

city has a population of about three quarters of a million, and appears to be a very "go-ahead" place. The medical faculty, which is large and active, is housed in fine buildings after the old spacious Spanish style, with a huge portico and massive marble staircase. The theater where I lectured was large and ornate but had good acoustic properties. I was much struck with the dissecting room, which was a veritable hive of industry, for there are large numbers of students of both sexes, and subjects are plentiful. I must say that I never saw more beautiful dissections in any "rooms" that I have ever visited. There is also a good and quite large anatomic museum. Testut is the usual textbook, but the clinicians complain that the students are expected to spend far too much time in anatomic study and that the subject is presented in too much detail. In nearly all the medical schools that I visited in South America the only whole time professors were the physiologists, so that it was surprising to hear that it was the extent of the anatomic teaching that appeared to be the more criticized. The large hospital is a very old building, also in the Spanish style, but it and the other hospitals are to be replaced by a modern medical center which is now in process of erection and where the buildings tower so high as to be a landmark from all over the city. Nearby is the new municipal Hospital for Infectious Diseases, with a fine range of laboratories for the public health work of the community. Prof Dr Horacio Garcia Lagos is head of the surgical department of the principal hospital, and in his service I saw many remarkable examples of hydatid disease, which is still one of the commonest of all the conditions with which they have to deal. It was interesting to see 2 patients operated on by the method of marsupialization, and, though I was struck by the powerful suction pump which was used for evacuating the parasites, I could not help feeling that such a machine might be dangerous in the hands of any but those who are very familiar with its proper use. They use a 2 per cent concentration of the standard (40 per cent) solution of formaldehyde very freely, not only to inject into the cyst before incision but to soak the gauzes which are packed about. Of course all branches of surgical work are represented, and I saw much of interest in genitourinary and bone work. As in Buenos Aires, the relations of the assistants with their chief seemed very cordial, and under his stimulating aegis much good work is being accomplished. The professor has large clinical classes, and the students did not seem to mind that most of the time allotted to his lecture was spent in addressing me in English. It was refreshing to meet Professor Navarro, who, at 76 years of age, is still doing full work in his surgical service and holding the attention of his classes. They have a special night emergency service for the hospitals, and after 8 30 p m all cases of acute disease are dealt with in one institution, special surgeons being appointed for

this purpose The British Hospital is quite an old institution with a fine reputation The management wisely includes on the staff one of the most respected of the university professors, Dr Horacio Garcia Lagos, which brings to the institution an academic status often lacking in the smaller hospitals

Montevideo owes a great deal to the wise guidance, enthusiasm and generosity of H B M Minister Mr E Millington-Drake In his efforts for the welfare of the people he is ably supported by his wife, Lady Effie, and the new maternity wing, which is her gift to the British Hospital, is complete and well designed and will be a great acquisition to the city Incidentally, let me say that in South America the advantage of maternity departments in connection with hospitals is being widely appreciated

Throughout the republics football appears to have taken the place of bull fighting, and one was astonished to see a new stadium which is said to be capable of seating 90,000 people, and which is furnished with its own first aid post and hospital

The activities of the cultural societies is marked both in Buenos Aires and in Montevideo In both cities I lectured to large audiences, mostly composed of the inhabitants, who study English with avidity in the classes arranged by the society

The next visit was to Rosario, a large port on the Parana river three and a half hours by rail from Buenos Aires The city claims half a million inhabitants who are largely occupied in the grain and cattle trades The principal hospital is old and dull, but the surgical side is very active, and I shall never forget the beautiful gastrectomy which I saw carried out with local anesthesia by Prof Dr Oscar Cames The professor makes a great feature of getting his patients up very early after operations, and I saw a man walking about, dressed in his ordinary clothes, two days after an extensive gastrectomy, which had also been carried out with local anesthesia When operating for renal calculus they always take a roentgenogram of the exposed kidney The plate, of a very "quick" variety, is enveloped in sterile wrappings and is actually held against the kidney during the very short exposure which is all that is necessary The plate is developed at once, they say that it requires only an extra four minutes and that the method often proves very helpful Many of the patients come from the campo, and diseases and injuries are apt to be far advanced before they reach the hospital The medical school is large and active, and there one found Professor Lewis with a complete department of physiology In the town there is a private hospital which is a veritable Mayo Clinic in miniature, and in the library there it was interesting and stimulating to find that English medical books were very popular

Cordoba, the next stopping place, is not quite such a large town, and is situated 432 miles from Buenos Aires. It is an old city, and the University is proud of the fact that it was the first in the republic and can look back on three hundred years of useful history. Originally a Jesuit college, it possesses a fine old library and a wonderful senate house, where the stalls for the professors are made of beautifully carved solid mahogany. The principal hospital is of the same old Spanish type with which one had become familiar, but it is to be gradually replaced by new pavilions. One of these pavilions is already finished and houses three departments of hospital activity, each on its own floor. We saw the throat and ear department, which is in charge of Dr. Heriberto Wilson. There everything was of the latest, and I was particularly struck by the rooms for the staff, including a departmental library, a lounge, and study rooms, all in addition to the ample suite provided for the professor himself.

Prof. P. L. Mirizzi is of course very well known in connection with his work on cholangiography carried out at the time of operation, and one was shown a wonderful collection of lantern slides illustrating the use of the method in all kinds of cases. Though it was Saturday afternoon, I found the department of physiology at work and was told that in the Argentine the day is not recognized as an academic holiday. I have never seen a department better equipped, in spite of the fact that it was housed in the oldest type of building imaginable, but the plans for a new building are now drawn up, and when complete the Physiological Institute ought to be very fine indeed. Although most of the instruments were from Germany, probably about a third were of English design and manufacture, and it was encouraging to notice a large proportion of English journals and books in the departmental library. Generally speaking, the Argentines are largely pro-British and are much attracted by our methods and our culture.

It was from Cordoba that we made the journey by plane over the Andes. This meant that part of the flight was at a height of between 15,000 and 20,000 feet, but, except for a slightly unpleasant sensation in the ears, it was just as comfortable as sitting in a very well sprung and luxurious motor car. But the grandeur of the Cordillera cannot be appreciated on a journey accomplished so easily, and as a corrective it is necessary to read Darwin's description of his crossing on muleback as related in the "Voyage of the Beagle." On arrival at Santiago we were courteously met by Dr. Fernando Opazo, who came to welcome us on behalf of the university. It was unfortunate that our visit happened to coincide with a great public holiday, which interfered seriously with the work of the hospitals. Nevertheless, we made a considerable tour of many institutions and were struck by the spacious

grounds in which they were situated. The hospital for accidents ("traumatology") is in a new building and is arranged after the style of the similar hospital presided over by Bohler in Vienna. The patients are accommodated in a number of small wards. Skeletal traction is largely employed, and compound fractures are treated without any dressings and certainly seem to do very well. Some very badly injured patients come from the campo and illustrate the difficulties of transport in a country with few railways and poor roads. In the Children's Hospital one saw a great deal of interest, acute osteitis and bone tubercle appeared to be very prevalent. The arrangements of the "Assistance Publique" impressed me very much. There are three principal centers, and all are arranged on much the same plan. The idea is that any sort of emergency case can be taken to these centers, where there is always a competent medical staff on duty. These physicians are all on the staffs of other hospitals and take two and one-half hour periods of duty in rotation throughout the twenty-four hours. Both medical and surgical emergencies are recognized, and the organization is served by an excellent ambulance service. Like "Maxim's," they never close, but the most striking feature is the fact that from about 8 p. m. until 8 a. m. the ordinary hospitals do not take emergencies, which during that period must perforce go to the "Assistance Publique," so that the ordinary hospital services and their patients are not disturbed during the hours of repose. Here they are dealt with, and at the earliest opportunity (it may be within a few hours or it may be after a few days) they are transferred to complete their recovery to the hospital in the district to which they belong. On admission to the station of the "Assistance" they first go through the cleansing department, where road dirt etc. is removed and the patient is washed and provided with hospital garments, and here the preliminary records are made. The operating theaters are always "set" for an operation, so that all that need be done is to remove the towels covering the sterilized instruments, lotion bowls etc., which are laid out in readiness. The records appeared to be most complete, special care being taken with the after-progress. All requisitions are carefully checked so that waste and extravagance can be eliminated. If the system works as well as it has been devised, then it must be good indeed. At a hastily convened meeting of the Society of Hospital Surgeons there was an enthusiastic audience eager to hear something of the progress of British surgery.

The journey home, up the west coast of South America, provided an opportunity for short visits to many places of much interest in several republics. I was particularly struck in the smaller places, like Antafagasta in Chile and Bueno-Ventura in Colombo, with the Oriental slums, small houses principally built of wood framing and completed with



corrugated iron or broken-up kerosene tins, which were eloquent testimony to the difficulties connected with the preservation of public health in such places. On the other hand, there were always one or more cinemas, however small and primitive, and I was reminded of the possibilities for public health propaganda which they might provide. If, for instance, films could be shown directed to instruction with regard to the prevention of malaria, cholera, typhoid and lesser diseases, it could do nothing but good and might prove invaluable. That this sort of propaganda is appreciated was suggested by the number of rather crude health posters which one saw displayed in various places. The consideration of this problem reminds me of the plan I saw in operation in Aden about three years ago. There the Port Sanitary Officer, Colonel Phipson, I M S, had a gramophone record made dealing with the simple measures that ought to be taken to prevent the various infective diseases which are liable to overrun such places with such tragic results. The record was produced in English, Arabic, Hindustani and Somali and was sold at a very cheap rate to the people, for many of the natives possess gramophones. The impression gained at a cinema may be vivid, but after all it is probably evanescent, and similar precise information which can be reiterated over and over again will surely make an appeal which, if not quite so graphic, may at least be looked on as of enormous supplemental value. I should like to suggest that the educational value of the cinema and the gramophone ought to be borne in mind by those who are concerned with health problems. The general observation suggested by the sort of tour with which I have dealt suggests the practical value of first-hand knowledge of the conditions existing in other countries. It certainly teaches one that physicians in other lands are only too anxious to be made familiar with the British point of view and are eager to discuss the facilities for the visitor from overseas who steps into Britain's medical circles. In Germany medical travel, at least for South Americans, is subsidized on every hand. There is the further advantage that the syllabus of the courses to be held is published long ahead, so that any one contemplating a visit will know what can be had in the way of lectures and demonstrations, perhaps six months before the time of the proposed visit. Since information about the activities of the medical institutions in Britain are not available in any one government or other central department, a foreigner is often at a loss to know to whom he is to apply for information, and the sooner we establish in London *one* really complete central bureau of medical information the sooner will this defect be rectified.

There is a great desire in South America for British publications, both books and periodicals, and for British drugs and instruments. The establishment of more scholarships in our medical schools and research

laboratories, such as those already endowed by the British Council, would also be welcome. Those who have already come over to England with university scholarships have suggested that the scope and details of the work to be done should be settled beforehand and that the student should receive help in mundane matters concerning the cost of travel, lodgings, etc. These things could best be arranged through a well regulated interchange of information, such as could be conducted through the suggested central bureau. One of the best of all methods for securing mutual advantage would be the interchange of assistants, and there one gathered that most of the difficulties would occur on our side in connection with the regulations of the General Medical Council. Attempts should continue to be made, however, to overcome these difficulties, because there is no doubt that the mutual advantage would be great. The student from South America who ardently desires to come to this country is not usually a man of means, and he can make the journey only at a considerable sacrifice either on his own part or the part of his parents, and they are anxious that such sacrifice should be made to the best advantage. Let me now say that the impression left by the British visitors who had preceded me was very vivid, and one heard much about Arbuthnot Lane, Lord Moynihan and Lord Dawson. Further, I should like to acknowledge gratefully the great assistance which I personally received from our Diplomatic Missions not only in the Argentine and in Chile, but in Uruguay, in the person of Mr. Millington-Drake, who does so much to promote international cultural relations.

# PHYSIOLOGIC SPHINCTER OF HEPATIC BILE DUCT

P L MIRIZZI, MD

CÓRDOBA, ARGENTINA

The purpose of this paper is to discuss the significance of cholangiograms obtained during operation which, in association with other circumstantial facts, prove the existence of a physiologic sphincter of the hepatic duct above the point of junction with the cystic duct

## PHYSIOLOGIC SPHINCTER

Contraction of the hepatic duct may be constantly observed cholangiographically during an operation. It takes place immediately above the crossing of the hepatic and cystic ducts and can be clearly seen when the walls of the ducts are elastic and thin. Neither total nor partial contraction is observable when the excretory passages are either dilated or thickened. In order to prevent artificial dilation of the biliary tract and any possible spasmodic reaction at the level of Oddi's sphincter, iodized poppyseed oil is injected at the rate of 1 cc a minute to a total dose of 3 cc in three minutes. Contraction is observable only when the iodized oil passes through the cystic duct slowly and in a small amount. If distention of the ducts occurs, as a result of a too large or a too rapidly injected dose, it is possible that the phenomenon cannot be seen even though an opaque substance more fluid than iodized poppyseed oil (such as colloidal thorium dioxide, skiodan or hippurate) is used. I intended to look at the hepatic duct during operation in a series of procedures in order to follow the behavior of the duct. However, I desisted from doing so because the structure is deeply situated, especially in obese, muscular patients like those on whom the operations were performed, and any maneuver at the hepatic hilus would have been dangerous. "*Primum non nocere*"

## EXISTENCE OF TWO EXCRETORY SYSTEMS

The contractile mechanism of the hepatic bile duct functions when the gallbladder spontaneously empties itself. In the contractile phase the gallbladder-cystic duct-common bile duct system is the only one which can be visualized. The phenomenon is clearly seen if iodized oil is allowed to pass spontaneously from the gallbladder through the cystic duct into the common bile duct without any maneuver which may force passage of the substance to the bile ducts. A few minutes after injection

of the oil the substance fills the common bile duct, but it does not pass into the intrahepatic branches of the biliary tree. The phenomenon is also observable in animal experiments.

In 1 of the cholangiographic observations which were made during the operation, iodized poppyseed oil was injected into the gallbladder and forced to pass to the cystic duct by means of mild compression of the gallbladder. The opaque substance passed violently to the whole biliary tree, the ampulla of Vater was open, and the intrahepatic branches of the biliary tree as well as the hepatic and common bile ducts were



Fig 1—Cholangiography during operation. Iodized poppyseed oil was injected into the gallbladder (G). There was a strong contraction at the crossing. The intrahepatic bile ducts and the proximal segment of the hepatic duct (H) were filled with oil. The common bile duct (C), dilated to the volume of a little finger, easily emptied its contents into the duodenum (Du) through the papilla of Vater (P). (The patient was M. S., a woman aged 26. She was admitted to the hospital in April 1935. She had been operated on for chronic appendicitis at the age of 18 years. She had had the first hepatic colic one year previously, followed by subjaundice and urticaria. The crises were repeated. Operation was performed with the aid of spinal anesthesia. There was cholecystitis, without concretions. The structure contained stagnated bile.)

dilated. Contraction was restricted to the cysticohepatic-common bile duct crossing (fig 1).

In the second clisé, taken ten minutes later, the intrahepatic branches were still filled with iodized oil, and the proximal segment of the hepatic

duct was dilated, whereas the terminal segment of the duct, near the crossing, was in a state of contraction. The gallbladder and the cystic and common bile ducts together formed a separate excretory system. The oil progressed slowly through the common bile duct, the diameter of which was greatly reduced. The substance was eliminated drop by drop through the papilla of Vater into the duodenum (fig 2).

The relative independence of the two coordinated excretory systems was shown by a new series of roentgenograms, which showed active filling of the gallbladder by iodized poppyseed oil. I have observed several times that any resistance at the distal third of the common bile duct produces peristalsis of the duct for as long as it is tonic, by which

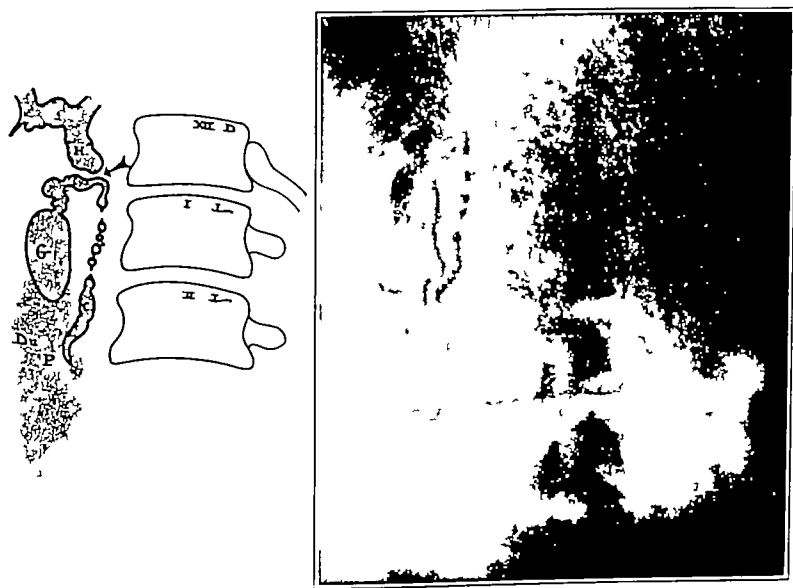


Fig 2—Cholangiography during operation. The roentgenogram was obtained ten minutes after the operation. The intrahepatic bile ducts and the proximal segment of the hepatic duct (*H*) were dilated, retaining all the iodized oil because of contraction of the distal portion of the hepatic duct (*H*). The gallbladder (*G*) made a system of evacuation with the common bile duct (*C*), the diameter of which was reduced to that of a quill. The oil was eliminated drop by drop through the papilla of Vater (*P*) into the duodenum (*Du*).

movement the column of oil ascends toward the crossing and drains into the cystic duct. The contraction of the hepatic duct prevents further progress of the opaque substance. This clearly shows the indirect protecting role of the hepatic duct, which favors repletion of the gallbladder with bile during the intervals of digestion (when the papilla of Vater is closed) as well as in any circumstance which changes the internal pressure of the common bile duct.

ABSENCE OF REFLUX OF OPAQUE SUBSTANCE BY  
PROPER DERIVATION OF SUBSTANCE

In general, when iodized poppyseed oil is directly injected either into the cystic duct or into the gallbladder itself, the upper branches of the biliary tract are partially injected with the substance. Notwithstanding the fact that the opaque substance progresses through the cystic duct slowly and regularly (as though it were being eliminated by the duct drop by drop) and independent of the mildness of the compression exerted on the gallbladder (when the substance is injected into the structure), a portion of the opaque substance overcomes the contraction

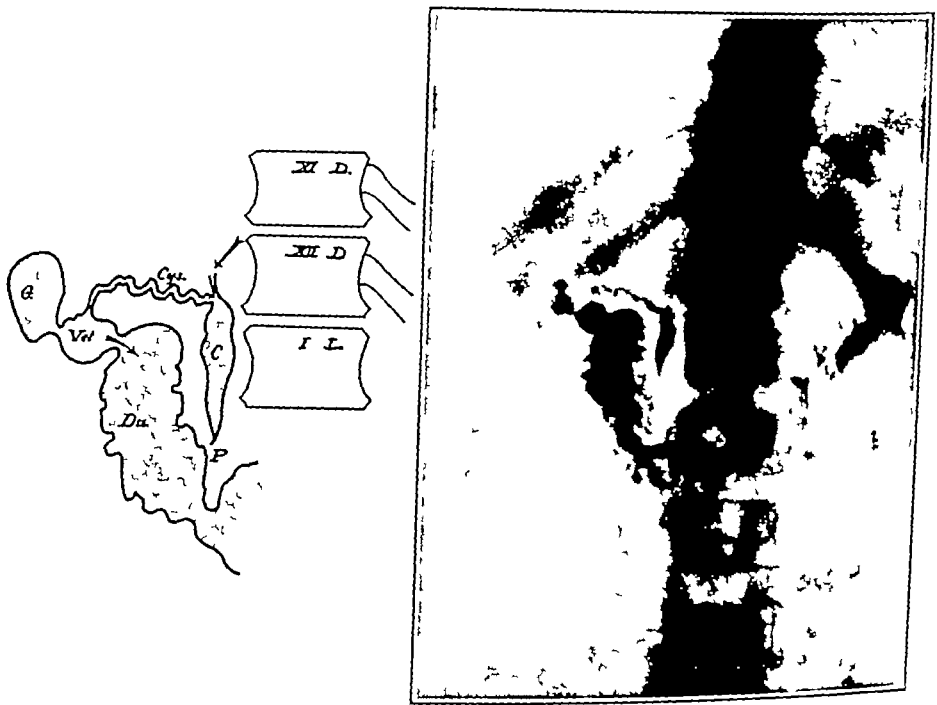


Fig 3—Cholangiography during operation. Iodized poppyseed oil was injected into the gallbladder (G). The opaque substance passed into the duodenum (Du) partially through the fistula which existed between the vestibule (Vet) and the duodenum (Du) and partially through the cystic duct (Cys), the common bile duct (C) and the papilla of Vater (P). The intrahepatic tree was not injected. The oil could not force its passage into the hepatic duct. (The patient was M. C., a woman aged 44, who was admitted in November 1936. The first hepatic colic had appeared twenty-five years previously, during the puerperium. Acute crises had appeared eleven years previously and had been repeated. During the last crises frequent vomiting had occurred and fever and jaundice had appeared. Operation was performed with the aid of spinal anesthesia. Acute pericholecystitis and a cholecystoduodenal fistula were present.)

of the hepatic duct and passes into the intrahepatic branches of the biliary tree. On the other hand, the opaque substance does not pass into the intrahepatic branches if a safety valve exists immediately adjacent

to the crossing point and counterbalances excessive pressure. I obtained this type of verification cholangiographically in patients who were operated on for a fistula. A communication was established between the neck of the gallbladder and the duodenal bulb by means of a small orifice similar to the urethral meatus of an adult. Ten cubic centimeters of iodized poppyseed oil was injected into the gallbladder. The structure was gently compressed in order to facilitate passage of the opaque substance into the biliary tree. A portion of the opaque substance passed to the duodenum through the fistula and another portion to the cystic duct—common bile duct system. The upper branches of the biliary tree

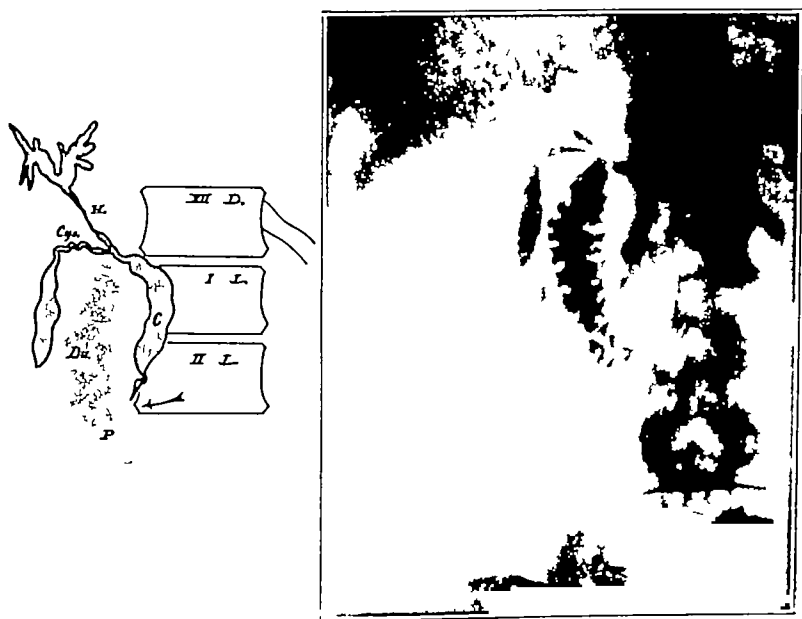


Fig 4—Cholangiography during operation (stenosing pancreatitis). Iodized poppyseed oil was injected through the cystic duct (*Cys*). The common bile duct above the stricture, was moderately dilated and filled with oil. The hepatic duct (*H*) was contracted. A large amount of oil passed through the papilla of Vater (*P*) into the duodenum (*Du*). (The patient was R. P. de Z., an obese woman aged 38, who was admitted in March 1935. During the last eleven years she had been suffering from intermittent crises of pain in the epigastric region and the right hypochondriac region. Sometimes the crises were followed by fever and jaundice. The zone of the pancreas and the common bile duct was painful on palpation. Operation was performed with the aid of spinal anesthesia. The calculous gallbladder was removed.)

were not invaded. There was sufficient contraction of the hepatic duct in this case to prevent the column of oil from ascending, and the excess passed through the fistula, which played a secondary neutralizing part (fig 3). There is no other plausible explanation for the phenomenon

The same phenomenon is observed when communication between the cystic duct and the duodenum is artificially established<sup>1</sup> In the course of an operation I found the stump of a dilated cystic duct (improperly called neogallbladder) The operation was performed because of sub-intrant pain after cholecystectomy Iodized poppyseed oil was injected into the stump (which was dilated to the size of an adult thumb) It showed the intrahepatic branches, which were dilated, the common bile duct, which was undulated from active peristalsis, and the presence of reflux in the duct of Wirsung A laterolateral cysticoduodenostomy was made, after which a Petzer sound was left in the dilated stump

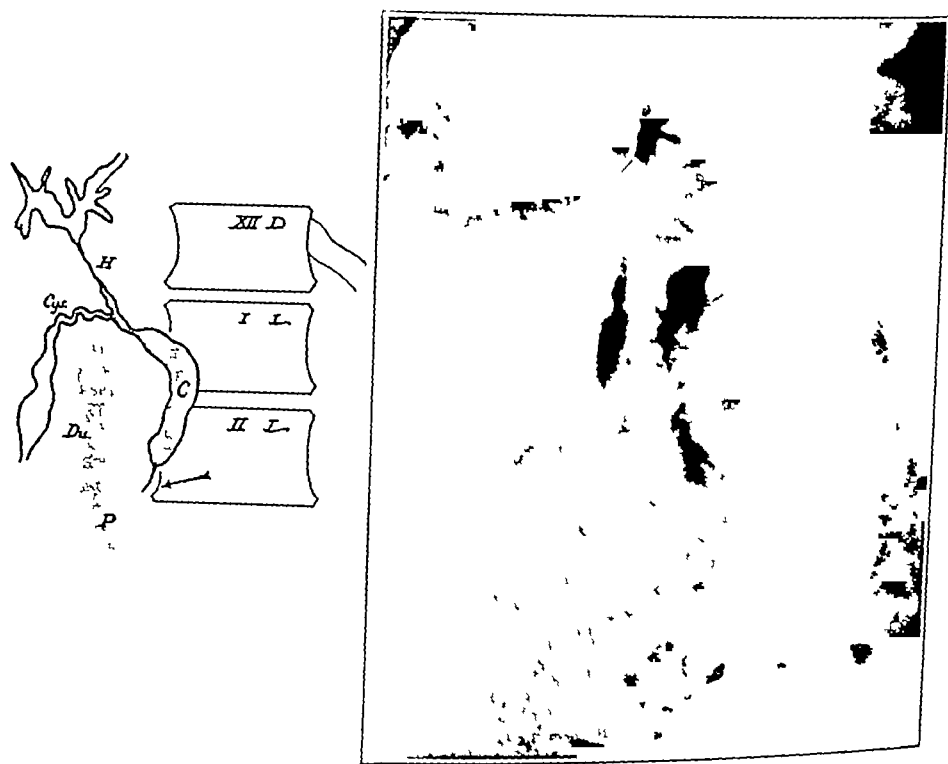


Fig 5—Cholangiography during operation The roentgenogram was obtained fifteen minutes after the operation The opaque substance in the common bile duct (C), which actively moved in peristalsis, was trying to subdue the obstacle The filiform strictured zone is visible in the illustration

Forty-eight hours later 10 cc of the oil was injected through the sound into the stump, as had been done in the course of the operation The clisé obtained during the injection did not show any reflux of the substance toward the upper branches of the biliary tree The phenomenon proved once more that as soon as a neutralizing derivation of the excess either of pressure or of injected oil is established, the contractile mechanism of the hepatic duct begins to function

1 Mirizzi, P L Dyskinesie und Gallenblasenregeneration Cystico Duodenostomie, Deutsche Ztschr f Chir 245 156, 1935



The common bile duct empties into the cystic duct when there is any resistance at its distal third. The phenomenon is frequently observed in the course of operations for calculous chronic cholecystitis when there is a stricture at the distal segment of the common bile duct near the papilla of Vater and the pancreatic duct in the absence of bile concretions. Figures 4 to 7 are explanatory. They show the picture in a case of stenosing pancreatitis following calculous cholecystitis in which cysticoduodenostomy was performed.

From these observations it is evident that contraction of the hepatic duct opposes progress of the opaque substance toward the intrahepatic

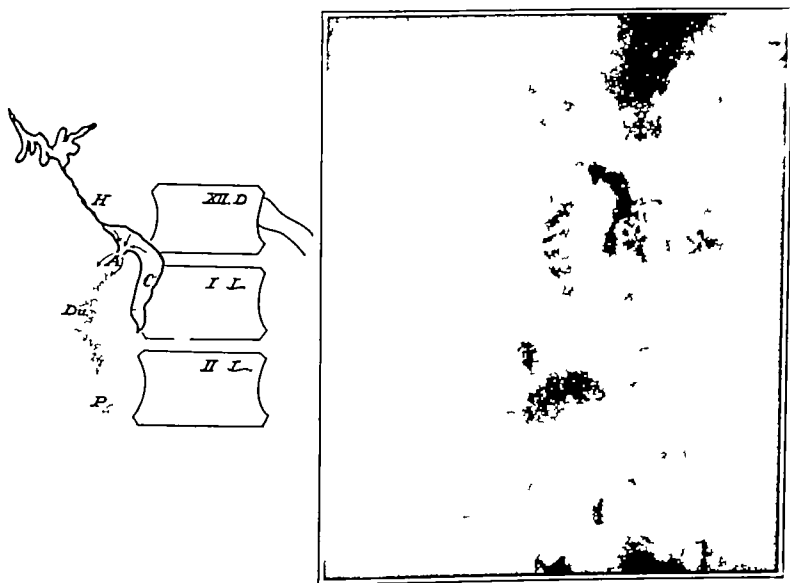


Fig 6—Cholangiography during operation. A cysticoduodenostomy was made. The transpancreatic segment of the common bile duct is not visible in the illustration. The main bile passage, between the point of contraction at the hepatic duct (*H*) and the stricture, at the level of the pancreas, was injected and in peristalsis iodized poppyseed oil passed through the anastomosis (*A*) into the duodenum (*Du*).

branches of the biliary tree, forcing the oil in the common bile duct to pass to the duodenum through the anastomosis. The phenomenon, which agrees with the normal physiology of the hepatic and common bile ducts, has been repeatedly verified by experimental proof of the existence of a contractile mechanism at the junction of the hepatic duct which plays a primary role in the excretion of bile. Section of the hepatic bile duct in biliary-intestinal anastomoses favors duodenal reflux. Certain techniques of anastomosis (Alessandri), which make sectioning

of the anterior wall of the hepatic and common bile ducts necessary, seem improper because of the frequency with which reflux of the duodenal content through the anastomosis and toward the biliary tree establishes itself<sup>2</sup>

In the only case in which I followed this technic (for derivation of the bile), duodenal regurgitation was observed. The same occurrence has been reported in the literature (Valdoni) with this type of anastomosis. Longitudinal section of the hepatic duct suppresses the defensive contraction of the duct and favors duodenobiliary regurgitation.



Fig 7—Cholangiography during operation. The roentgenogram was obtained sixty minutes after the operation. Iodized poppyseed oil accumulated at the distal part of the hepatic duct (*H*) and the proximal segment of the common bile duct opposite the anastomosis (*A*) through which the opaque substance passed into the duodenum (*Du*).

#### PRACTICAL CONCLUSIONS

Cholangiographic study during operation clarifies several direct and indirect facts which prove the existence of a physiologic, anatomic neurosympathetic center in the wall of the duct or in its proximity. The center controls the function of the hepatic bile duct in coordination with the distal segment of the common bile duct and the sphincter of Oddi.

<sup>2</sup> Mirizzi, P. L. L'infection ascendante dans les anastomoses bilio digestives (apropos d'une observation), *Mem Acad de chir* 63 907, 1937.

Because of these observations and from clinical experience I believe that integrity of the hepatic bile duct must be respected so as not to destroy contraction of the physiologic sphincter of the duct in creating a biliary-intestinal anastomosis. The same criterion compelled me to perform, systematically, low transverse choledochotomy in all cases of lithiasis of the common bile duct. In all cases, but especially in those in which contractility of the hepatic duct is evident, the operation is performed immediately on the upper edge of the duodenum.

# LIGATION OF THE INFERIOR VENA CAVA

JAMES L WHITTENBERGER, M D

AND

CHARLES HUGGINS, M D

CHICAGO

Sudden obstruction of the inferior vena cava above both kidneys has been found to be fatal in dogs, whereas ligation is well borne when carried out below the renal veins. A method is described whereby complete closure of the vena cava above both renal veins was successfully carried out.

Ligation of the inferior vena cava produces various effects, depending on factors which affect the adequacy of collateral circulation, namely, the site of ligation, suddenness of occlusion and species and age of the animal<sup>1</sup>. The site of ligation relative to the kidneys is of prime importance because of the enormous blood flow through the kidneys, it has been found that survival depends largely on the degree of compromise of the renal circulation<sup>2</sup>.

There is general agreement that ligation of the renal vein is followed by progressive atrophy of the kidney and decrease or complete cessation of all urinary secretion, invariably in cats<sup>3</sup> and rabbits<sup>4</sup> and nearly always in dogs<sup>5</sup>. Microscopic studies have shown that the damage is greatest in the tubules, the glomeruli being preserved relatively intact<sup>6</sup>.

Ligation of the vena cava just above the renal veins in the dog almost always results in death<sup>7</sup>, Polkey<sup>2</sup> had 1 of 5 dogs survive this

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From the Department of Surgery of the University of Chicago

Aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago

1 (a) Pleasants, J H. Johns Hopkins Hosp Rep **16** 363, 1911 (b) Addison, T, and Lew, W. Proc Soc Exper Biol & Med **42** 602, 1939 (c) Montemartini, G. Policlinico (sez chir) **41** 593, 1934

2 Polkey, H J. Urol & Cutan Rev **33** 294, 1929 Pleasants<sup>1a</sup>

3 Zuckwer, J T. Am J Path **2** 57, 1926

4 Chin, R. Tr Jap Path Soc **28** 277, 1938

5 Harrington, S W. Effect on Kidney of Various Surgical Procedures on the Blood Supply, Capsule, and on Ureters, Arch Surg **2** 547 (May) 1921

6 Bender, J A, and Hayman, J M, Jr. Proc Soc Exper Biol & Med **32** 1018, 1935

7 Zuckwer<sup>3</sup> Pleasants<sup>1a</sup> Montemartini<sup>1c</sup>

ligation In the rat, however, similar ligation in young animals causes only a transient period of renal insufficiency followed by complete recovery in almost all cases, the mortality rate from the procedure was found to increase with the age of the rats<sup>1b</sup>

Abundant evidence exists that ligation of the vena cava below the renal veins is not a serious surgical procedure either in man or in the lower animals<sup>2</sup> Edema or slight albuminuria may develop, but neither is common ,

In this study, the venous drainage of one kidney was impeded, and we were interested in (a) the functional changes which occurred due to this venous obstruction, (b) the compensatory changes which resulted in the unobstructed kidney and (c) the possibility of ligating the vena cava subsequently above both renal veins

#### METHODS

Female dogs kept under standard laboratory conditions were used in all experiments, all operations were performed with ether anesthesia and with aseptic technic The animals were first prepared by transplanting the ureters with a small cuff of bladder into the skin of the corresponding groin fold When ready for experimentation the dog was placed on its back on a table, and urine was allowed to collect in the natural anatomic pocket of each groin Little restraint was usually necessary, the dogs were kept comfortable by frequent rest periods The urine was removed by pipets, the method making possible quantitative collection of the secretion from each kidney without the use of catheters and experimentation on one kidney with the other reserved as a control Before each observation period food was withheld for eighteen hours, water was given freely one hour before the collection of urine to insure adequate urine flow It was interesting to note that fright or other distress caused almost immediate cessation of urine flow, sometimes for a minute or more. An ammoniacal dermatitis developed in a few dogs but was usually temporary

Oblique inter-renal ligation consisted in placing a silk ligature diagonally around the vena cava in such a way (fig 1) that one renal vein was drained above it and the other below, free communication remaining between each renal vein and the adjoining vena cava After ligation venous pressures were measured in the veins of the leg with a saline manometer connected to a needle in the vein as a direct method. In an acute experiment it was found that pressure in the veins of the leg closely reflected pressure in the obstructed vena cava below the ligature Arterial pressures were measured directly in the femoral vessels, without anesthesia, by a mercury manometer

Renal function was studied by creatinine and phenol red clearances, rate of excretion of phenol red and measurement of volume and total solids It is well established that the exogenous creatinine clearance is a measure of glomerular filtration in the normal dog kidney<sup>8</sup> Sterile solutions of creatinine in doses large enough (usually 200 mg per kilogram) to elevate the blood plasma level to 10 to

<sup>8</sup> Smith, H W The Physiology of the Kidney, New York, Oxford University Press, 1937, p 96

20 mg per hundred cubic centimeters were given subcutaneously. One hour later, when the blood level had become more or less stable, clearances were started. Urine was collected for periods of ten minutes with rest intervals between. Samples of venous blood were taken at the middle of each period or interpolations made to that point. The syringe was moistened with a drop of saturated potassium oxalate, and the blood was gently transferred to a tube containing another drop of oxalate. Creatinine determinations were made according to a slight modification of Folin's alkaline picrate method<sup>9</sup> on diluted urine and on plasma from which the proteins had been precipitated by tungstate, with use of the Evelyn photoelectric colorimeter (Wratten filter no 75 + 9785), and all clearances were calculated as plasma clearances. Accuracy of the method was checked by recovery from blood of known amounts of creatinine which had been added. Urine flow in our experiments was

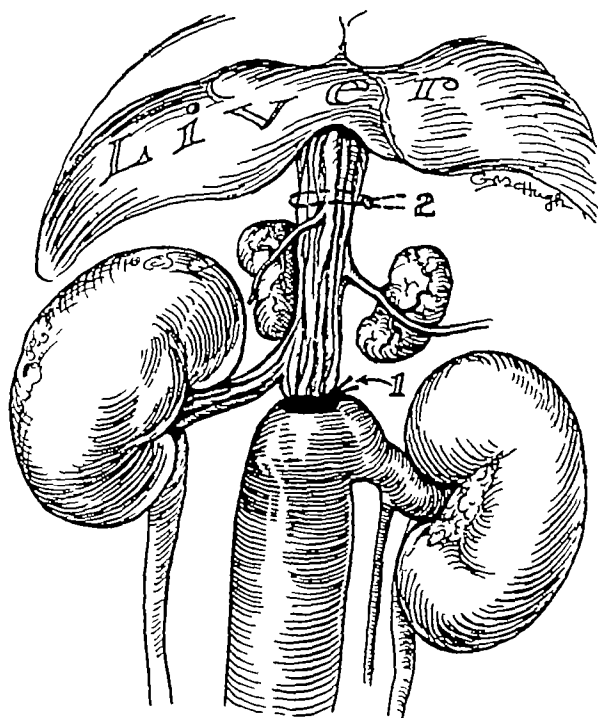


Fig 1—Oblique inter-renal ligation of the inferior vena cava. A ligature is so placed (1) that one renal vein drains below the ligature while the other drains above it. Subsequently high ligation of the vena cava (2) can be carried out successfully.

sometimes as low as 0.1 cc per minute from one kidney, but Shannon<sup>10</sup> has shown that the creatinine clearance is independent of urine flow, even at very low levels of flow.

Tubular action was studied by the rate of excretion of phenol red and by phenol red clearances done simultaneously with creatinine clearances. Just before the creatinine clearances were started, a single injection of alkaline phenol red was given intravenously in amounts sufficient to raise the plasma level initially to 3 to 6 mg per hundred cubic centimeters, clearances were done on the falling blood level.

<sup>9</sup> Folin, O., and Wu, H. *J Biol Chem* 38:98, 1919.

<sup>10</sup> Shannon, J. A. *Am J Physiol* 114:362, 1936; *Proc Soc Exper Biol & Med* 33:474, 1935.

Since phenol red interferes with the colorimetric determination of creatinine, a special logarithmic graph (fig 2) was made to show compensation for interference at various concentrations of phenol red. The phenol red content of the plasma was determined by alkalinizing the plasma diluted with saline solution to the appropriate concentration and reading in the Evelyn colorimeter with filter 540, using a blank of diluted plasma taken before the injection of dye. Hemolysis was infrequently obtained. No attempt was made to differentiate the glomerular filtration fraction of the plasma phenol red clearance.

The rate of excretion of phenol red was measured after intravenous injection of 6 mg of the dye, urine was collected for two fifteen minute periods. Urine was examined microscopically and tested for albumin occasionally. Total solids were determined by accurately weighing 1 cc of urine before and after drying at 105 C overnight.

### RESULTS

*A Ligation of the Vena Cava Above Both Renal Veins*—Two dogs in which the vena cava was tied above both renal veins died in shock five and ten hours respectively after operation. In the leg the venous pressure was 26 cm of water in

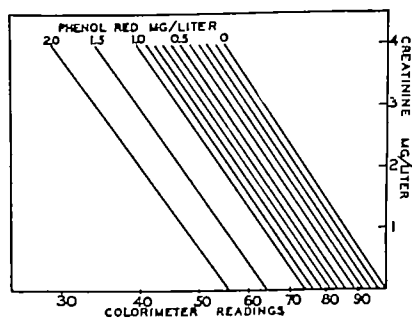


Fig 2—Semilogarithmic graph for determination of creatinine in the presence of phenol red

1 dog, the rectal temperature was 98.6 F, the body surfaces were cold, and the skin was cyanotic over the lower half of the body. At autopsy the kidneys were tense and dark red, the vessels of the lower half of the body were engorged, and the soft tissue was edematous and mottled in places with petechial hemorrhages. In both dogs small amounts of dark, bloody urine were observed in the bladder.

*B Ligation of One Renal Vein*—A renal vein was ligated in each of 2 dogs. In 1 the obstructed kidney within two hours was secreting only a small amount of coagulated and fibrinous pale pink urine. The urine the next day was clear in the gross but continued to be minute in amount and very dilute. It contained many epithelial cells. In two months there was no sign of recovery. The obstructed kidney in a second dog was at first putting out small amounts of visibly bloody urine but recovered rapidly until, at the end of two weeks, it was functionally equal to its mate. Compensatory hypertrophy of the normal kidney was marked in both dogs, persisting in the first and disappearing in the second dog as the damaged kidney returned to normal. For changes in creatinine clearance in the second dog, see figure 3.

*C Oblique Inter-Renal Ligation of the Vena Cava*—Inter-renal ligation was performed in 5 dogs (fig 1) Invariably the immediate result was almost complete suppression of urine on the obstructed side, with a consequent drop almost to zero of all clearances and of phenol red excretion Albumin and gross blood appeared in the urine of the obstructed kidney in all dogs, decreasing markedly after a day or two In 4 of the dogs recovery of the obstructed kidney began promptly and progressed steadily until (within three to six weeks) function was fairly good, although it never equaled that of the normal kidney Small amounts of albumin and a few red and white blood cells could constantly be found in the urine, which was dilute, total solids being approximately one-fourth normal (fig 4) Intravenous administration of physiologic solution of sodium chloride produced

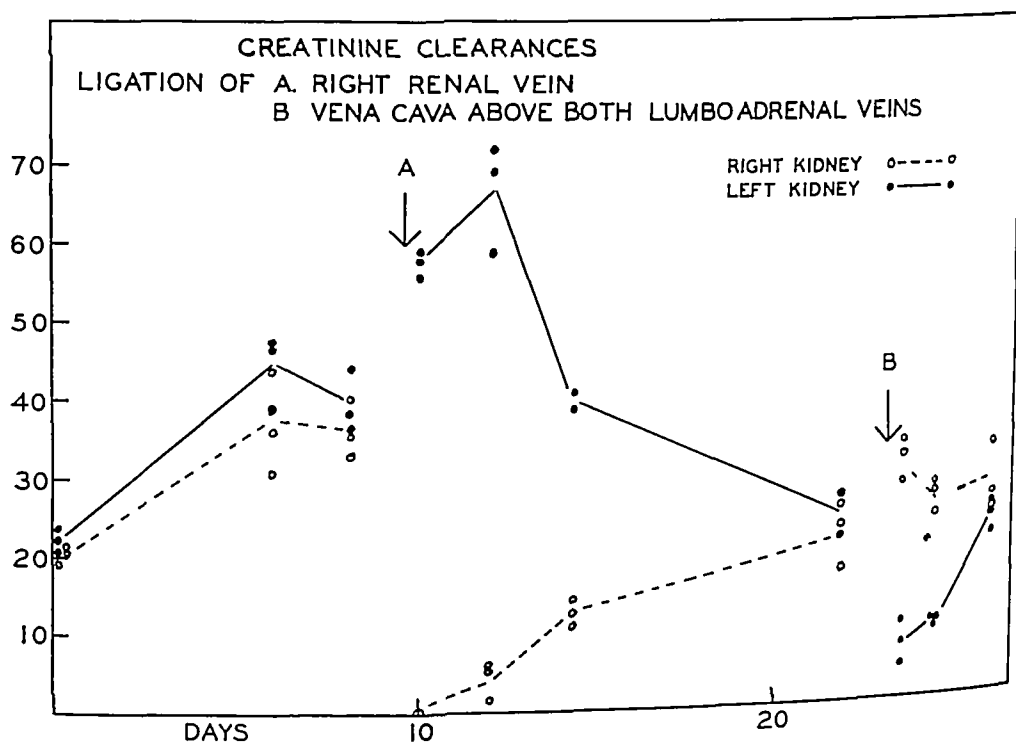


Fig 3—Changes in creatinine clearances after ligation of the right renal vein and of the vena cava above both renal veins fifteen days later. Three clearances were done at each test. Note the increase in function of the normal kidney and the depression and recovery of the obstructed kidney. The ordinate units are cubic centimeters per minute, the abscissa is time in days.

marked increases of volume secreted by the damaged kidney without altering clearance values.

In 1 dog, however, no recovery occurred in the damaged kidney throughout thirteen and one-half weeks of observation. A very slight increase in function occurred when the opposite, normal kidney was removed.

Concurrently with depression of the kidney obstructed by oblique ligation was a uniform increase in function of the unobstructed kidney. Increase in all clearance values and volume output appeared within two to three hours after ligation. Following day values were usually less, but thereafter they increased daily. For approximately two weeks, not much difference being observed between increases



phenol red and creatinine clearance values. In the dogs in which recovery of the injured kidney occurred, the functional hypertrophy decreased synchronously with the increase on the recovering side (fig 5)

D *Ligation of the Vena Cava Above Both Renal Veins Subsequent to Oblique Inter-renal or Renal Vein Ligation*—Ligation of the vena cava above both renal

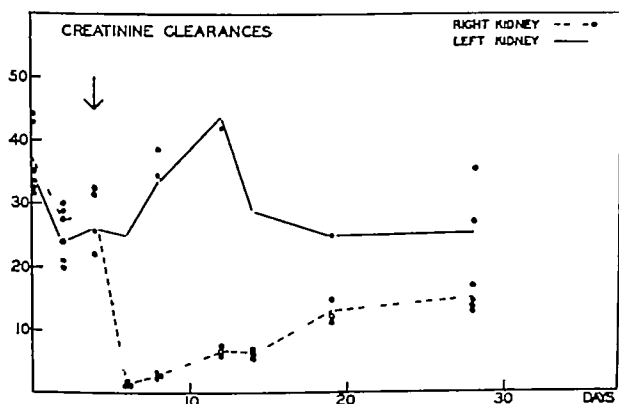


Fig 4—Changes in creatinine clearances after oblique inter-renal ligation of the vena cava above the right renal vein. The ordinate units are cubic centimeters per minute, the abscissa is time in days. Note the depression of the obstructed kidney, followed by progressive recovery, the compensatory increase in function of the normal kidney decreased with return of function of the other kidney.

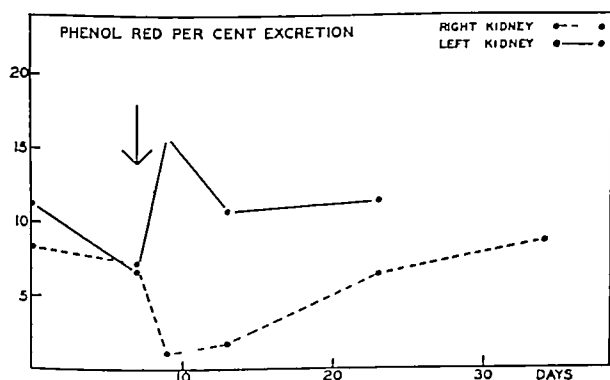


Fig 5—Changes in phenol red excretion after oblique inter-renal ligation of the vena cava above the right renal vein. The ordinate is the percentage of 6 mg of phenol red eliminated within thirty minutes of initial venous injection. The abscissa is time in days. Complete recovery occurred in the obstructed kidney.

veins was performed in 2 dogs after inter-renal ligation and in 2 dogs after ligation of one renal vein. In no case was the procedure fatal, resulting only in relatively mild depression of the normal kidney and extrarenal symptoms, which will be mentioned later. Complete recovery of the slightly damaged kidney occurred.

*E Extrarenal Effects of Ligation of the Vena Cava*—Ligations at the sites mentioned produced prompt cyanosis of the lower half of the body in all animals, accompanied by dilatation of small veins in the skin, elevated venous pressure and usually slight edema. The cyanosis regularly disappeared within twenty-four hours and the edema within three or four days. Progressive enlargement and tortuosity of the larger cutaneous veins were the only permanent signs of obstruction. Elevation of venous pressure in the hindlimbs was 25 to 40 cm of water, compared with 5 to 10 cm in the forelimbs, decrease in pressure occurred until normal values were reached, usually within a week. The arterial pressures were all normal.

*F Hypertrophy in an Explanted Kidney*—In a dog with one kidney explanted by Alving's method<sup>11</sup> it was possible to observe changes in size resulting from compensatory hypertrophy and ligation of the vena cava. After ligation of the renal vein one kidney became practically functionless, but the explanted kidney did not increase in size, although its function as measured by clearances was steadily increasing. Ligation of the vena cava above both renal veins caused a slight enlargement, which had entirely disappeared within eighteen hours.

*G Autopsy Observations*—In 3 dogs with oblique inter-renal ligation and in 1 with ligation of a renal vein followed by ligation of the vena cava, autopsy revealed complete obliteration of the vena cava below the ligature, only a fibrous cord marking the course of the vessel, the obstructed renal vein in each case was completely fibrosed. In 1 dog with oblique inter-renal ligation of the vena cava and one with ligation of the renal vein followed by ligation of the vena cava the vena cava was patent both above and below the ligature, which was intact, although the obstructed renal veins were thrombosed. Collateral channels involved chiefly anastomoses of capsular veins with lumbar, lumboadrenal and ovarian veins and the vena cava when that vessel remained patent. One kidney which had no return of function was very small, weighing only 10 Gm, it was pale and firm, without dilated capsular veins. Otherwise gross and microscopic studies of the kidneys were noncontributory.

#### COMMENT

It had been intended to study excretory tubular mass and renal blood flow in obstructed kidneys, but renal damage was found to be so gross that it was useless to apply the finer discriminations in the use of clearances to determine those points.

Our results confirm those of Montemartini,<sup>10</sup> Polkey<sup>2</sup> and others, who have found that ligation of the vena cava above both renal veins is nearly always fatal. We cannot draw conclusions from two complete ligations of the renal vein, but one of them resulted in excellent recovery of renal function.

Inter-renal ligation produces, at least for a period before thrombosis occurs, acute passive congestion of the kidney similar to that produced by Rowntree, Fitz and Geraghty<sup>12</sup> by partial occlusion of venous drainage. They found that slight constriction of a renal vein sometimes

11 Gorden, W., Alving, A. S., Kretzschmar, N. R., and Alpert, L. *Am J Physiol* **119** 483, 1937.

12 Rowntree, L. G., Fitz, R., and Geraghty, J. T. *The Effects of Experimental Chronic Passive Congestion on Renal Function*, *Arch Int Med* **11** 121 (Feb) 1917.

produced mild polyuria, in our experiments passive congestion, although probably more severe than theirs, has always produced oliguria, amounting at times almost to anuria. Toth,<sup>13</sup> by having animals breathe oxygen at low tension, has shown that oliguria usually results from anoxia in anesthetized dogs, whereas polyuria is the usual response in unanesthetized ones. Winton,<sup>14</sup> in the heart-lung-kidney preparation, demonstrated that a rise in renal venous pressure to 20 mm of mercury decreased the output of urine 30 per cent. Schmidt and Chen<sup>15</sup> elevated intra-abdominal pressure to 27 to 28 mm of mercury and found that urine flow stopped unless a glass cannula was inserted into the renal vein. They, as well as Winton,<sup>16</sup> found that saline diuresis easily overcame these pressures. Lasher and Glenn,<sup>17</sup> who anastomosed the renal artery and vein, found cessation of urinary flow.

Studies of explanted kidneys are of value in studying the problems of compensatory hypertrophy. Moberg,<sup>18</sup> using rats, found evidence that anatomic hypertrophy may occur independently of functional hypertrophy and that degenerative changes always occurred in hypertrophied tubules. MacKay, Addis and MacKay,<sup>19</sup> Allen<sup>20</sup> and others have shown that a high protein diet increases anatomic hypertrophy. Mason, Blalock and Harrison,<sup>21</sup> using their direct method of measuring blood flow from the two renal veins, found that unilateral nephrectomy caused a 30 per cent decrease in blood flow.

Our observations revealed an immediate marked increase in the measurements of function of the normal kidney, in glomerular filtration as well as tubular activity. That this increase represents opening up of unused nephrons is doubtful, in view of White's evidence that all glomeruli of the dog function simultaneously.<sup>22</sup> Compensatory hypertrophy, beginning promptly, increased steadily for about two weeks before leveling off except in dogs in which the damaged kidney recovered. The explanted kidney of 1 dog did not increase in size while

13 Toth, L. A. *Am J Physiol* **119** 127, 1937

14 Winton, F. R. *J Physiol* **72** 49, 1931

15 Schmidt, C. F., and Chen, K. K. *Proc Soc Exper Biol & Med* **21** 414, 1923

16 Winton, F. R. *Physiol Rev* **17** 408, 1937

17 Lasher, E. P., Jr., and Glenn, F. *Effects on Kidney and Blood Pressure of Artificial Communication Between Renal Artery and Vein*, *Arch Surg* **38** 886 (May) 1939

18 Moberg, E. *Acta path et microbiol Scandinav*, 1936, supp 31 p 1

19 MacKay, L. L., Addis, T., and MacKay, E. M. *J Exper Med* **67** 515, 1938

20 Allen, R. B. *J Urol* **34** 553, 1935

21 Mason, M. T., Blalock, A., and Harrison, T. R. *Am J Physiol* **118** 739, 1937

22 White, H. L. *Proc Soc Exper Biol & Med* **41** 190 1939

undergoing functional hypertrophy Soskin and Saphir<sup>23</sup> have reported that prevention of anatomic hypertrophy by imprisoning the kidney in a cast was fatal to unilaterally nephrectomized animals

In spite of interference with venous drainage, no hypertension was observed in any of our dogs This observation confirms those of Eichelberger<sup>24</sup> on hydronephrosis, contrasting with those of Katz and his co-workers<sup>25</sup> Bell and Pederson<sup>26</sup> found that hypertension lasting several months regularly developed in rabbits in which a renal vein was almost completely occluded and collateral circulation was not permitted to develop

#### SUMMARY

Individual renal function was studied in dogs with cutaneous ureterostomies, by means of creatinine and phenol red clearances Remarkable parallelism amounting almost to equality of function exists in the paired normal kidneys

Ligation of the vena cava above both renal veins in 2 normal dogs produced surgical shock which was fatal in five and ten hours respectively

In 5 dogs oblique inter-renal ligation of the vena cava was performed, one renal vein being included below the ligature, causing venous congestion in the corresponding kidney, while venous drainage from the opposite kidney was unimpaired In all dogs there was immediate depression of function on the obstructed side, in 4 of the 5 eventual functional recovery was almost complete, and in the fifth no recovery occurred Coincident with the depression on the obstructed side, there was marked functional hypertrophy on the normal side, this increase persisted as long as the other kidney was damaged and disappeared if and when function of the other returned These dogs survived subsequent ligation of the vena cava above both renal veins, and the operation produced minimal effects on the kidneys

Complete ligation of the main renal vein in 1 dog resulted in functional depression with recovery of the kidney in thirteen days, while in another dog permanent impairment resulted In each dog subsequent ligation of the vena cava above both renal veins was well tolerated

Measurements of an explanted kidney undergoing hypertrophy showed that functional hypertrophy may occur without commensurate anatomic hypertrophy

Autopsy studies showed that the recovery of renal function after venous obstruction depends on the development of an adequate collateral

23 Soskin, S, and Saphir, O *Am J Physiol* **101** 573, 1932

24 Eichelberger, L *Proc. Soc. Exper. Biol. & Med.* **42** 249, 1939

25 Megibow, R S, Friedberg, L, Rodbard, S, and Katz, L *N. Engl. J. Med.* **282** 1111, 1970

26 Bell, E T, and Pederson, A H *Ann. Int. Med.* **4** 227, 1930

renal venous drainage    Allowing time for development of collateral circulation to one kidney made possible high ligation of the vena cava in dogs

#### CONCLUSIONS

Ligation of the vena cava above both renal veins causes death in dogs in a few hours from surgical shock due to accumulation of blood from two kidneys, in the posterior portion of the body. When oblique ligation of the vena cava between the kidneys is done, allowing development of collateral veins in one kidney, subsequent complete high ligation of the vena cava is well borne, it is not followed by shock or interference with renal function in the kidney with adequate venous drainage.

# SICKLE CELL DISEASE

## PATHOGENIC, CLINICAL AND THERAPEUTIC CONSIDERATIONS

JULIUS BAUER, M D  
LOS ANGELES

Since the original description of sickle cell anemia by Herrick in 1910,<sup>1</sup> sufficient data have been accumulated to permit certain statements concerning the pathologic physiology involved and to warrant certain practical conclusions as to the management of the condition. The purpose of this contribution is to put on record additional data derived from personally studied material, as well as additional conclusions, chiefly therapeutic, derived from these data and from other data already on record in the literature.

It was striking to observe, in the material examined, that

1 Sickle cell anemia is not infrequently entirely overlooked by the clinician and is discovered only by the pathologist at necropsy. The diagnosis is established by the observation of a small, markedly atrophied spleen, which consists merely of a mass of partially calcified fibrotic tissue. This type of spleen is unknown in any other diseases except those in which complete destruction of the splenic blood supply has occurred.

2 Errors of diagnosis are not infrequent. The enlarged heart, systolic murmur and accentuated second pulmonic sound observed in the patient with sickle cell anemia may lead to an incorrect diagnosis of rheumatic mitral lesion. Sickle cell anemia may account for hypertrophy of the right side of the heart without a valvular lesion. It may be the underlying cause of ulcers of the leg. It may give rise to pain, presumably of rheumatic origin, in the muscles, bones and joints. It may also cause so-called abdominal crises which may be diagnosed as acute appendicitis or perforated peptic ulcer and for which operation may be done unnecessarily or even with fatal consequences.

3 Patients with sickle cell anemia present very poor medical and surgical risks. They may succumb to such a relatively simple disease as acute catarrhal colitis. They may lose their lives from such a simple

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From the Department of Medicine of the School of Medicine of Louisiana State University and the Charity Hospital of Louisiana at New Orleans.

1 Mason, V R. Sickle-Cell Anemia, in Downey, H. *Handbook of Hematology*, New York, Paul B Hoeber, Inc, 1938, vol 3, p 2329.

procedure as appendectomy or hernioplasty because their disease was not recognized and they were not properly protected against the risk inherent in it. They may die after a blood transfusion correctly done with compatible blood.

#### NATURE OF THE SICKLE CELL TRAIT (SICKLEMIA)

Sickle cell anemia is one of several recognized types of inborn, hereditary (constitutional) abnormalities of the red blood corpuscles, including, in addition, constitutional hemolytic jaundice (Minkowski-Chauffard), ovalocytosis (Dresbach), and Mediterranean erythroblastic anemia (Cooley's disease).

Certain facts concerning the sickling phenomenon are now clearly established.<sup>2</sup> Sickling is dependent solely on the red blood cells. It does not depend on any peculiarity of the plasma. It is readily demonstrated by a simple laboratory technic. It is markedly enhanced both in vitro and in vivo by lack of oxygen and by an increased supply of carbon dioxide.<sup>3</sup> The phenomenon is reversible, and exposure of the sickle cells to an atmosphere rich in oxygen permits them to resume their spherical form. Sickling undoubtedly occurs in the circulating blood and may be seen even in immature nucleated red cells. Because the sedimentation velocity of the affected cells is diminished, the sedimentation rate may be normal even in the presence of marked anemia.<sup>4</sup> Sickling cells do not show any rouleau formation.<sup>5a</sup> They are definitely more resistant to hypotonic salt solution than are normal red blood cells, and in some persons some sickle cells do not exhibit hemolysis even in distilled water.

Several important facts concerning the sickling phenomenon are still unknown. Thus it is not possible to say at this time whether the filaments produced by normal living red corpuscles are the agents which cause the sickling deformation of certain erythrocytes (Auer<sup>5</sup>). It is not known what kind of peculiar and specific "surface phenomenon"<sup>6</sup> is the operative factor. Finally, investigations on the electric charges of sickling cells, which may offer a clue for elucidation of the problem, have not yet been carried out.

2 (a) Diggs, L. W., and Bibb, J. The Erythrocyte in Sickle Cell Anemia, *J. A. M. A.* **112** 695 (Feb. 25) 1939. (b) Mason.<sup>1</sup>

3 Hahn, E. V., and Gillespie, E. B. Sickle Cell Anemia, *Arch. Int. Med.* **39** 233 (Feb.) 1927. Scriver, J. B., and Waugh, T. R. Studies on Case of Sickle Cell Anemia, *Canad. M. A. J.* **23** 375, 1930.

4 (a) Bunting, H. Sedimentation Rates of Sickled and Non Sickled Cells from Patients with Sickle Cell Anemia, *Am. J. M. Sc.* **198** 191, 1939. (b) Diggs and Bibb.<sup>2a</sup>

5 Auer, J. Structure and Function of Filaments Produced by Living Red Corpuscles, *Am. J. M. Sc.* **186** 776, 1933.

6 Huck, J. G. Sickle Cell Anemia. *Bull. Johns Hopkins Hosp.* **34** 335, 1923.

It may be accepted as an established fact that sickle cell anemia is due to an inborn and constitutional abnormality of erythropoiesis. The essential abnormality is that variable numbers of red cells are produced which exhibit characteristic deformities under conditions which do not alter normal red cells (Mason). The constitutional sickle cell trait is transmitted by heredity as a dominant mendelian characteristic (Huck<sup>6</sup>). That the trait is not recessive is demonstrated by an observation of King and Janeway.<sup>7</sup> In a family in which both parents were affected, only four of the six children inherited sickle cell anemia, whereas a recessive characteristic would have been transmitted to all six children.

If sickle cell disease, as will be pointed out later, is due to the deleterious consequences resulting from the abnormal constitutional trait sickle cell anemia, one might expect to find other constitutional abnormalities rather frequently in persons affected with it as compared with normal persons. This is not the time to consider whether the sickle cell trait represents one of the degenerative stigmas characterizing what I<sup>8</sup> have termed "status degenerativus," but certain suggestive evidence might be briefly listed here.

1 A 10 year old Negress who died of massive necrosis of the renal cortex due to impaction of sickled cells in the small renal vessels also presented a thyroglossal cyst and multiple congenital cysts and abnormal fissures in the lungs.

2 A 4 year old Negro child who succumbed unexpectedly to simple catarrhal colitis exhibited at autopsy sickle cell disease and feminine pseudohermaphroditism. The child had been brought up as a boy, and hypoplasia of the penis and a mild degree of hypospadias had been diagnosed ante mortem. Autopsy revealed female internal genital organs, a communication between the vagina and the urethra and an absence of testicular tissue.

3 A 70 year old Negress with sickle cell anemia presented at post-mortem examination an atrophic spleen weighing 16 Gm and multiple leiomyomas of the stomach.

4 Somewhat similar observations are on record in the literature. Ryerson and Terplan<sup>9</sup> described in 1 of their cases "a tendon-like thickening of the lower part of the right aortic valve, apparently

<sup>7</sup> King, J. T., and Janeway, C. A. Sickle Cell Anemia with Cardiac Complications, *Internat Clin* 3 41, 1937.

<sup>8</sup> Bauer, J. Vorlesungen ueber allgemeine Konstitutions- und Vererbungslehre, ed 2, Berlin, Julius Springer, 1923, Konstitutionelle Disposition zu inneren Krankheiten, ed 3, Berlin, Julius Springer, 1924.

<sup>9</sup> Ryerson, C. S., and Terplan, K. L. Sickle Cell Anemia. Two Unusual Cases with Autopsy, *Folia haemat.* 53 353, 1935.



corresponding to an abnormal fibre of the specific bundle" Harden<sup>10</sup> reported oxycephaly and congenital abnormalities of the retinal blood vessels in 2 brothers affected with sickle cell anemia. Haden and Evans,<sup>11</sup> in reporting hereditary "flexion deformity of the little finger" (camptodactylism) in 2 sisters of Sicilian descent with sickle cell anemia, wrote "The familial occurrence of the flexion deformity of the finger in this family is of great interest, since s c a is considered a similar anatomic defect in the shape of the erythrocyte" It is not inconceivable that persons with such crooked fingers may also have other "crooked" structures and functions, though I am not inclined to accept the word as literally as these authors did. It must be noted, however,<sup>12</sup> that crooked little fingers were first described by Adams in 1890 and that Landouzy, who first applied the term camptodactylism to the deformity,<sup>12</sup> considered it a constitutional stigma.

It should be emphasized that the observations which have been cited are merely suggestive and are not put forward as evidence of an association of sickle cell anemia with other constitutional stigmas.

#### PATHOGENESIS OF SICKLE CELL ANEMIA

That sickle cell anemia is hemolytic (produced by an exaggerated destruction of red blood corpuscles) is capable of clinical and anatomic proof. Clinical proof is supplied by the acholuric jaundice which regularly accompanies it, the indirect van den Bergh reaction in the blood serum, the increased output of urobilin in the urine and in the stools, and such signs of stimulated erythropoiesis as an increase in the number of reticulocytes and nucleated red cells. Anatomic proof of the increased destruction of red blood cells is supplied by the evidences of increased activity of the reticuloendothelial system in the spleen, the liver, the bone marrow and the lymph nodes, proliferation of the Kupffer cells, which occasionally show marked phagocytosis of the erythrocytes, and large deposits of hemosiderin found in various organs.

The mechanism of the destruction of blood associated with sickle cell anemia is still unknown, but it seems clear that it differs from that of the abnormal hemolysis of hemolytic jaundice. In the latter disease the probable operative factors are the increased fragility of the spherocytes and the increased activity of the spleen. In the presence of sickle cell anemia, on the contrary, the red cells are even less fragile than normal.

10 Harden, A. S. Sickle Cell Anemia, *Am J Dis Child.* 54 1045 (Nov) 1937

11 Haden, R. L., and Evans, F. D. Sickle Cell Anemia in the White Race, *Arch Int Med* 60 133 (July) 1937

12 Aschner, B., and Engelmann, G. *Konstitutionspathologie in der Orthopaedie*, Berlin, Julius Springer, 1928

ones, and in cases of the advanced condition the spleen seems almost completely exhausted and its functional capacity practically lost. The anemia, nevertheless, may become severe.

As a matter of fact, both Cooley's anemia and the anemia due to ovalocytosis are also hemolytic. The osmotic resistance is increased in the former condition and is at least not diminished in the latter. Furthermore, it must be remembered that even in cases of hemolytic jaundice the destruction of the blood in the body is not caused by exposure of the erythrocytes to hypotonic solutions. An increased osmotic fragility merely indicates that the red corpuscles possess a faulty structure or an abnormal composition. It has long been known that the resistance of red blood cells varies with different agents and under different circumstances. The resistance toward lysolecithin of the red cells has been found increased in some cases of sickle cell anemia, which is in contrast to the diminished resistance observed in cases of constitutional hemolytic jaundice (Singer<sup>13</sup>). In the presence of sickle cell anemia the erythrocytes have been shown to have a somewhat diminished resistance to mechanical trauma as compared with normal controls.<sup>14</sup> On the other hand, their demonstration in the circulating blood twenty-one days after they had been transfused into normal persons (Sydenstricker) would seem to indicate,<sup>1</sup> even though reliable normal control studies are not available,<sup>11</sup> that they are not liable to premature destruction.

Mason<sup>1</sup> assumed that in cases of sickle cell anemia the mode of disintegration of the red cells may be active phagocytosis of defective erythrocytes by macrophages, with liberation of hemoglobin. Such a hypothesis is scarcely in accord with his own statement that there is "no evidence of perverted activity of phagocytes in the disease."

On the basis of both clinical observations and histologic studies, I am convinced that the extensive hemolysis which accompanies sickle cell anemia is due to a relatively simple process. It is caused by the mechanical impaction of masses of deformed red blood cells in the smaller blood vessels of various organs. This impaction, with the subsequent hemolysis of the resulting conglutinated masses, is responsible for the further pathologic changes and for the clinical symptoms of sickle cell anemia.

The massive hemolysis associated with sickle cell anemia can reasonably be explained on a morphologic basis. The most striking feature of the disease is the engorgement of small blood vessels with

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13 Singer, K. The Lysolecithin Fragility Test, *Am J M Sc.* **199** 466, 1940

14 Dekker, H J N. The Fate of the Transfused Red Blood Cells, *Acta med Scandinav* **99** 587, 1939

sickled red corpuscles The liver and, in the initial stages, the spleen are most frequently affected The sinusoids of the spleen are for the most part compressed and relatively empty, and the pulp is engorged with masses of erythrocytes, which are greatly elongated, pointed, curved and bizarrely shaped Sometimes the capillaries of the malpighian bodies are enlarged and appear as multiple small varices containing pools of blood lying within them or at their edges <sup>16</sup>

Microscopically the appearance of the spleen in the initial stage of sickle cell anemia is similar to its appearance in cases of hemolytic jaundice except for the characteristic shape of the red cells In the later stages there are certain fundamental differences 1 The characteristic transformation of the enlarged spleen into a fibrotic, extremely atrophied organ does not occur with hemolytic jaundice as with sickle cell anemia 2 Except in the spleen, no engorgement of other organs with red cells is noted in cases of hemolytic jaundice In the presence of hemolytic jaundice the lungs, lymph nodes, kidneys and liver are normal except for some hyperactivity of the Kupffer cells in certain exceptional cases <sup>16</sup>

The tremendous engorgement of the reticulum meshes has been variously explained Diggs <sup>15a</sup> considered it to be due at least partially to hemorrhages around the terminal arterioles, though, as Ryerson and Terplan <sup>9</sup> noted, it is extremely difficult to distinguish areas of actual hemorrhage from pools of blood in the distended reticulum meshes Rich <sup>17</sup> stated the belief that congenital malformations of the sinusoids account for a free escape of blood into the red pulp (which perhaps further supports the concept of "status degenerativus"), but Ryerson and Terplan <sup>9</sup> pointed out that the passage of blood from the sinusoids into the reticulum meshes may be a physiologic process rather than the result of a congenital defect

Engorgement with disfigured red blood corpuscles similar to that observed in the spleen is also encountered in the distended capillaries of the liver, lymph nodes, lungs, kidneys and other organs in cases of sickle cell anemia In a personally observed case the blood vessels of the cortical portions of both kidneys were filled with sickle cells so closely packed together as to resemble coagulum, though no fibrin could be found in the masses

15 (a) Diggs, L W Siderofibrosis of the Spleen in Sickle Cell Anemia, J A M A **104** 538 (Feb 16) 1935 (b) Jaffe, R H The Reticulo-Endothelial System, in Downey, H Handbook of Hematology, New York, Paul B Hoeber, Inc, 1938, vol 2, p 973 (c) Ryerson and Terplan <sup>9</sup>

16 Meulengracht, E Chronic Hereditary Hemolytic Jaundice, in Downey, H Handbook of Hematology, New York, Paul B Hoeber Inc, 1938, vol 3, p 2281

17 Rich, A R The Splenic Lesion in Sickle Cell Anemia, Bull Johns Hopkins Hosp **43** 398, 1928

Another rather constant observation in cases of sickle cell anemia is proliferation of the hepatic Kupfer cells and of the reticuloendothelial cells of the lymph nodes.

There can be little doubt that the abnormal configuration of the erythrocytes must be the cause of the engorgement which they produce in the small arterioles and capillaries<sup>18</sup>. The elongated, distorted red corpuscles cannot pass through the narrow vessels as readily as normal cells, and more or less marked stasis follows the attempted passage of great numbers of characteristically deformed cells. The engorgement is particularly frequent in those organs in which the rate of blood flow is unusually slow and the oxygen tension, as a result, is unusually low. It is for these reasons that the particular, though by no means the exclusive, sites of stagnation are the spleen, the liver and the lymph nodes. This concept, which has been supported by Diggs<sup>15a</sup> and Yater and Hansmann,<sup>18a</sup> is in my opinion the only satisfactory explanation of the microscopic observations associated with sickle cell anemia.

The essential pathologic process in sickle cell anemia, then, is the stagnation and conglutination of disfigured red corpuscles which has just been described. The serious consequences which follow can readily be deduced from one's knowledge of general pathology, that is, one's knowledge of the typical biologic reaction of the organism to long-standing circulatory stagnation. They include (1) thrombosis, (2) ischemia, necrosis and fibrosis, and (3) resolution of the red blood cells with subsequent anemia.

1 *Thrombosis*—Slowing of the blood stream predisposes to thrombosis, followed by endarteritis and infarction, which is a frequent observation in cases of sickle cell anemia. The arterioles of the spleen, the lungs and the brain are particularly likely to be affected. A somewhat different explanation, however, must be advanced for the obliterating endarteritis of the medium and large cerebral vessels described by Bridgers<sup>19</sup> in the case of a child affected with sickle cell anemia, as well as for the arteriolosclerosis observed by Yater and Hansmann<sup>18a</sup> in the pulmonary arteries. At present it is impossible to determine whether previous thromboses and the frequent biologic inferiority of the vascular system in the Negro race are to be considered as causative factors.

2 *Ischemia, Necrosis and Fibrosis*—Whether or not the circulatory stagnation caused by the deformed sickle cells results in actual thrombosis, the conglutination of the packed cells necessarily produces the same effects in the affected tissues. Ischemia, necrosis, endarteritis, fibrosis,

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18 (a) Yater, W. M., and Hansmann, G. H. Sickle Cell Anemia. A New Cause of Cor Pulmonale, *Am J M Sc* **191** 474, 1936. (b) Diggs<sup>15a</sup>

19 Bridgers, W. H. Cerebral Vascular Disease Accompanying Sickle Cell Anemia, *Am J Path* **15** 353, 1939.

hyalinization and deposition of blood pigment and calcium are characteristic of the transformation of the initially enlarged spleen into the atrophic, sclerotic organ observed later (Diggs<sup>13a</sup>) Analogous changes may take place in other organs In a case personally observed and previously referred to, the small blood vessels of the renal cortex were engorged with sickle cells, and massive bilateral cortical necrosis was a striking and unusual postmortem observation The clinical implications of this case are also worthy of mention The patient, a 10 year old Negress, was operated on for a thyroglossal cyst without recognition of her sickle cell disease After operation she showed signs of renal disease, and an antemortem diagnosis of acute nephritis was made Just before death the nonprotein nitrogen content of the blood was 120 mg per hundred cubic centimeters Actually the child died from an atypical sequela of her sickle cell trait It was not the anemia but the sickling of the red corpuscles which was responsible for the fatal outcome

3 *Resolution of Red Corpuscles and Anemia*—Stagnation and conglutination of red corpuscles, such as are seen in cases of sickle cell anemia, must eventually lead to disintegration of the corpuscles, again without regard to whether or not thrombosis develops There would seem to be no other pathologic state in which an engorgement of the small blood vessels of various organs, with subsequent stasis and impaction of erythrocytes, occurs to such a degree and for such long periods as in sickle cell anemia The disintegration of the conglutinated red cells sets free hemoglobin, which is transformed into the blood pigment found in various organs and into the bilirubin found in increased amounts in the blood serum The dead corpuscles and shadows finally disappear as the result of the phagocytic action of the reticuloendothelial cells, which are seen in full activity and proliferation in the spleen liver, bone marrow and lymph nodes The microscopic picture of the small, firm, fibrotic spleen associated with sickle cell anemia has been described by Diggs<sup>13a</sup>

The pulp, instead of being a mass of erythrocytes as in the early stages, is now a mass of reticulum between which the packed sickled cells lie in capillary-like spaces In some spleens the sinusoids are greatly dilated and tortuous and their endothelial cells are hypertrophied Pigment granules are conspicuous in the organizing lobules and there is phagocytosis of erythrocytes by macrophages Giant cells and branching filaments are occasionally seen

I have myself seen this microscopic picture and have also observed the proliferation of Kupffer cells in the liver and of the reticuloendothelial cells in the lymph glands "stuffed with disfigured erythrocytes," as described by Jaffe<sup>13b</sup>

If the concept of the pathogenesis of the anemia or sickle cell anemia which I have just set forth is accepted, it is clear that anemia is merely one of the disastrous consequences of the sickle cell trait and as a rule, not its most

dangerous consequence. The hemolytic anemia is merely the most obvious and most readily recognizable clinical sign of the ailment, which would more reasonably be termed sickle cell disease than sickle cell anemia.

Anemia, furthermore, is not one of the very early consequences of the disease. It develops only when the regenerative power of the bone marrow no longer has the ability to compensate for the increased number of red blood cells destroyed. As long as compensation exists, no anemia can be demonstrated, which is also the case with hemolytic jaundice and Cooley's disease. Microscopic signs of precipitated regeneration are found in both the circulating blood and the bone marrow in cases of sickle cell anemia. Direct involvement of the bone marrow by the fundamental process of sickle cell disease (that is, circulatory stagnation and its consequences) brings about a progressive impairment of the regenerative power of the bone marrow and enhances the development of anemia.

#### CLINICAL SIGNS AND SYMPTOMS

The clinical symptoms and signs of sickle cell disease are not difficult to explain in the light of the concept that the disease is due to conglutination of the deformed erythrocytes and to the consequences of this process. Certain of these clinical manifestations, while they are by no means specific, are of great value in arousing the suspicion that sickle cell disease may be present.

1. Slowly healing, nonvaricose superficial ulcers of the leg, which may be present even in childhood, are clinically important, even though neither the clinical appearance nor the microscopic structure shows specific features. The slow circulation in the lower limbs facilitates their development, but it is no more known whether or not thrombosis plays a role in their production (Diggs) than it is known whether temporary arteriolar and capillary engorgement with sickled cells is responsible. Similar ulcers have been observed in persons with constitutional hemolytic jaundice.<sup>20</sup>

2. Changes in the bones are less frequent than are ulcers of the leg, though the same rarefaction of the cancellous bones and the same "moth-eaten" and "hair on end" appearance of the skull are observed with sickle cell disease as with Cooley's erythroblastic anemia and, to a milder degree, with hemolytic jaundice,<sup>21</sup> and it is quite possible that

20 Taylor, E. S. Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, *J. A. M. A.* **112** 1574 (April 22) 1939. Leger, L. H., and Orr, T. G. Chronic Leg Ulcerations in Congenital Hemolytic Jaundice, *South M. J.* **33** 463, 1940.

21 (a) Gaensslen, M. Skelettveränderungen bei Blutkrankheiten, in *Libro de Oro dedicado al Dr. Mariano R. Castex*, Buenos Aires, 1938, vol. 2, p. 507.  
(b) Meulengracht.<sup>16</sup>

they may contribute, at least partially, to the "rheumatic" pains of which these patients complain. Such migrating pains in the bones, joints and muscles are far more frequent than are demonstrable osseous changes, and it seems entirely justifiable to classify them among the specific manifestations of the disease. This type of "rheumatoid pain" in cases of sickle cell disease would be somewhat related causatively to the hypertensive type of so-called "rheumatism" described many years ago.<sup>22</sup>

3 Rheumatoid and abdominal pains, which occasionally become excruciating (so-called abdominal crises) are characteristic. Thrombotic processes are believed to account for these manifestations. Vascular engorgement, however, with subsequent stagnation of the blood stream, may have a similar effect.

4 Cardiac symptoms and signs in patients with sickle cell anemia frequently simulate the effect of a mitral valvular lesion of rheumatic origin. Differential diagnosis is difficult if not impossible, as I have observed in several cases. The diagnosis is particularly difficult with patients who run a low grade fever and who complain of "rheumatic pains." Sickling, hemolytic anemia and a sedimentation rate within normal limits do not necessarily rule out a concomitant active or old rheumatic lesion of the heart, but in the majority of such cases a diagnosis of rheumatic valvular disease will probably be wrong.<sup>23</sup> Yater and Hansmann<sup>18a</sup> satisfactorily explained the cardiac signs associated with sickle cell disease by describing a noninflammatory "thromboangitis obliterans," capillary stasis and thrombosis in the lungs in 2 cases in which the diagnosis of mitral stenosis, made ante mortem, proved incorrect at autopsy.

5 The liver may be affected. Ryerson and Terplan,<sup>9</sup> for instance, have described a case of sickle cell disease in which subacute yellow atrophy of the liver was diagnosed clinically and demonstrated at autopsy. Such a "complication," to my mind, is not merely accidental. In microscopic preparations in cases of sickle cell disease I have observed not only distention of the hepatic sinusoids by packed sickle cells but definite signs of damage to the liver cells themselves. They may be somewhat compressed and in some areas may show vacuolization, fatty change and necrosis. Some cells may lose contact with the liver cell cords and lie separated and surrounded by proliferated Kupffer cells and perivascular accumulations of lymphocytes and mononuclear cells. Some degree of periportal fibrosis is frequently seen. It is not inconceivable that such an exceptionally extensive alteration of the liver cells may provide the

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<sup>22</sup> Bauer, J. Hochdruckrheumatismus. Verhandl. d. 33 Kongr. d. deutsch. Gesellsch. f. inn. Med., 1922, p. 436. Der sogenannte Rheumatismus. Dresden: Theodor Steinkopff, 1929.

<sup>23</sup> King and Janeway.<sup>7</sup> Haden and Evans.<sup>11</sup>

substratum for what is usually termed hepatitis (catarrhal jaundice) and might better be called hepatosis and that such a condition might eventually lead to acute or subacute hepatic atrophy

This type of hepatosis, usually of rather mild degree and course, probably occurs in association with sickle cell disease more frequently than is usually realized. Dale<sup>24</sup> reported a case of this association. A 14 year old Negress first gave a positive indirect van den Bergh reaction and later a biphasic reaction in the serum, the stool did not contain bile or the urine urobilin. A few days later both reactions became positive. The same author mentioned the occasional occurrence of a positive direct van den Bergh reaction in the serum of patients with sickle cell anemia, although as a rule this reaction is positive only in the indirect phase.

Another illustrative case,<sup>25</sup> still under observation at Charity Hospital of Louisiana at New Orleans, may be cited.

A Negress, first seen at the age of 19 years in April 1937, at that time was in a severe active phase of sickle cell disease. The red cell count was 752,000 and the white cell count 12,300 per cubic millimeter. An ulcer had been present on the right ankle for four months and healed only when the patient reached the latent phase, in September 1937. At that time there were 4,420,000 erythrocytes per cubic millimeter and 90 per cent hemoglobin (Sahli). During 1939 and 1940 repeated examinations showed the red cell count to be more or less constantly 2,500,000 per cubic millimeter and the hemoglobin 50 per cent. The icterus index during this period was 20, the value for serum bilirubin 4.8 mg per hundred cubic centimeters, and the van den Bergh reaction indirect positive.

The patient has had two definite attacks of hepatosis (catarrhal jaundice), diagnosed by a marked increase in jaundice, temporary enlargement of the liver, a temporary positive direct van den Bergh reaction in the blood serum and a positive hippuric acid reaction indicative of functional disturbance of the liver cells.

6 Other clinical manifestations are less frequent. Cerebral manifestations, usually diagnosed as thrombosis or intracranial hemorrhage, have frequently been reported within recent years.<sup>26</sup> The fundamental anatomic lesion seems to be the engorgement of greatly congested capillaries with sickled erythrocytes. Some type of thromboangitis obliterans, with multiple areas of perivascular hemorrhages and focal necrosis, could reasonably be considered a consequence of hemostasis and engorgement. Large subarachnoid hemorrhages and thrombosis of the dural sinus have

24 Dale, G. C. Sickle Cell Anemia, *South Med & Surg* 49 14, 1937

25 This case will be reported in detail by Dr. R. C. Lowe

26 Arena, J. M. Cerebral Vascular Lesions Accompanying Sickle Cell Anemia,

*J. Pediat.* 14 745, 1939. Yater and Hansmann.<sup>18a</sup> Bridgers<sup>19</sup>



also been observed. Massive necrosis of the renal cortex has previously been mentioned as the result of impaction of sickled cells in the small vessels of the kidneys.

#### RELATION OF SICKLING AND SICKLE CELL DISEASE

Whether sickle anemia invariably precedes the development of sickle cell anemia is still a matter of debate. Mason<sup>1</sup> stated that proof of the thesis is lacking and also expressed doubt whether sickle anemia persists through the life of the affected person. For my own part, on the basis of clinical and biologic evidence, I believe that sickle anemia is a necessary predisposing factor in the development of sickle cell anemia.

This point of view is in complete accordance with the established facts concerning other constitutional abnormalities of the red blood corpuscles. The spherocytosis and microcytosis characteristic of constitutional hemolytic jaundice, for instance, may be present without jaundice and without anemia in so-called compensated cases in families of persons suffering from this disease (Gaensslen,<sup>27</sup> Bauer<sup>8</sup> and others). An analogous "compensated" state has been described in connection with Cooley's disease without anemia (Wintrobe and others<sup>28</sup>), and in 1 case overcompensation seemed to exist. The patient had 6,440,000 red corpuscles per cubic millimeter of blood, and there were microcytosis, hypochromia, marked stippling of the red cells, "target cells," increased resistance of the erythrocytes to hypotonic saline solutions and splenomegaly. Similar observations have been made in cases of ovalocytosis, which usually represents a harmless abnormal constitutional variation in the shape of the red cells but which may lead to anemia in some persons.<sup>29</sup>

When and under what circumstances the sickle cell trait is converted into sickle cell disease is still not entirely clear. The sickle cell trait is found in about 7.5 per cent of North American Negroes, but these Negroes are chiefly of mixed blood, and no information is available as to the frequency with which it is found in pure bred Negroes in Africa. Only a certain proportion of persons who exhibit the trait, however, actually suffer from sickle cell anemia. Sydenstricker set the proportion at 1.5 per cent.<sup>1</sup> Dale<sup>24</sup> and Johnson and Townsend<sup>30</sup> reported a per-

<sup>27</sup> Gaensslen, M. Ueber haemolytischen Icterus, *Deutsches Arch. f. klin. Med.* **140** 210, 1922.

<sup>28</sup> Wintrobe, M. M., Matthews, E., Pollack, R., and Dobyus, B. M. A Familial Hemopoietic Disorder in Italian Adolescents and Adults. *J. A. M. A.* **114** 1530 (April 20) 1940.

<sup>29</sup> Mason, V. R. Ovalocytosis, in Downey, H. *Handbook of Hematology*, New York, Paul B. Hoeber Inc., 1938, vol. 3, p. 2349. Gaensslen<sup>27</sup>.

<sup>30</sup> Johnson, F. B., and Townsend, E. W. Sickle Cell Anemia. *South Med. & Surg.* **49** 377, 1937.

centage as high as 10 Huck,<sup>o</sup> by systematic blood tests, showed that in Negroes with sicklemlia but without clinical signs or symptoms of sickle cell anemia, sickling was observed in 25 per cent of the red cells. In persons with mild signs of the disease the proportion rose to 75 per cent.

The discrepancy in the estimates is apparently due to the highly variable course of the disease. Some persons die from it in early childhood, some live for decades in spite of recurrent acute attacks, and some never present any clinical evidence of the disease, which is demonstrated only by the characteristic observations at necropsy. Diggs,<sup>15a</sup> in this same connection, emphasized, I think correctly, that either a large and congested or a small and atrophic spleen may be found in children as well as in adults, "which indicates that the active disease may occur in varying age periods or that the rate of progression of the lesion is highly variable."

The first clinical manifestations of the disease may be preceded by some acute infectious disease or may be precipitated, as has already been pointed out, by some surgical procedure. Under these circumstances thrombosis is facilitated, and any factors which cause slowing of the circulation may also play a part in converting sicklemlia into sickle cell disease, provided a sufficient number of erythrocytes are affected with the pathologic trait.

From what has been said certain statements seem to be justified

- 1 The sickle cell trait shows individual differences in intensity, that is, in the number of affected cells

- 2 The mechanism which converts sicklemlia into sickle cell disease may be set into action if a sufficiently large number of cells are affected and if conditions particularly favorable for sickling are present

- 3 Such conditions include local or general anoxemia, infectious diseases, surgical procedures and other circumstances and factors which are known to slow the circulation of the blood

- 4 In view of these differences, it is easy to understand why sickle cell disease varies so widely as to age of onset, clinical picture and course

Sicklemlia, as has been pointed out, must be distinguished from true sickle cell disease. In the same manner, active and latent sickle cell disease with and without anemia must be distinguished from each other. The latent phase of the disease may be described as a condition of subjective health which represents a period of apparent recovery following a period of ill health due to the disease. At this time the only demonstrable signs are sickling of the red cells, anemia, which is usually mild, and bilirubinemia. A picture of this kind indicates that the patient is not merely predisposed to sickle cell disease but is actually affected with it.

It must be remembered, in the same connection, that sickling is a reversible phenomenon. That is why the observations at autopsy are

not constant. It is possible to find only the residua of the circulatory stagnation formerly present in the various organs. Not always does one find the engorgement with packed sickled cells where endarteritis, fibrosis and proliferation of reticuloendothelial cells indicate the presence of sickle cell disease. To put it another way, although autopsy often reveals merely a special stage of the disease, it practically always permits also conclusions as to its past course.

#### REPORT OF SPECIAL CASES

It occasionally happens that a cellular reaction produced by a pathologic process far surpasses the original aim of this reaction,<sup>31</sup> as the following case illustrates.

CASE 1—I T, a 33 year old Negro, had complained for three years of numbness in the legs, pains in the lower extremities and elsewhere, dyspepsia with occasional vomiting, abdominal pain, headache, vertigo, dyspnea on slight exertion, weakness and fatigue. He had had several epileptiform seizures and occasionally had low grade elevations of temperature. His chief complaint when he was first seen was of obstinate ulcers of the leg.

Physical examination revealed him to be anemic and subicteric, with a markedly enlarged heart and a blowing systolic murmur over the apex. Roentgen examination revealed considerable enlargement of the transverse cardiac diameter and unusual porosity of the skull, particularly in the frontal region. The electrocardiogram revealed no abnormalities. The blood pressure was 130 systolic and 80 diastolic.

Serologic tests for syphilis gave negative results, and examination of the cerebrospinal fluid revealed no abnormalities. The red cell count was 2,735,000 and the white cell count 13,000 per cubic millimeter of blood. The value for hemoglobin was 50 per cent (8 Gm). Polychromatophilia, anisocytosis and poikilocytosis were observed, and 80 to 90 per cent of the red cells showed definite sickling at the end of twelve hours in a wet preparation at 37 C. Numerous nucleated erythrocytes were present. On subsequent examinations the red cell count reached a minimum of 1,900,000 per cubic millimeter. The indirect van den Bergh reaction was positive, and the value for serum bilirubin 5.5 mg per hundred cubic centimeters.

The patient was given a transfusion when examination of the blood showed 2,300,000 red cells per cubic millimeter, 77 Gm of hemoglobin and a hematocrit value of 17.5 per cent. The temperature was 102 F and the blood pressure 122 systolic and 90 diastolic. When the patient had been given 200 cc. of cross-matched compatible blood by the direct method he complained of abdominal pain and dyspnea. The transfusion was stopped at once but death occurred unexpectedly five hours later.

*Postmortem Examination*—The spleen, which weighed 15 Gm., was highly atrophic, whitish and composed of fibrous trabeculae, with no remaining pulp. The liver, which weighed 3,200 Gm. was slate brown and markedly enlarged. On section the normal architecture was obliterated. The gallbladder was enlarged.

31 Bauer, J. Adaptation and Compensation as Origin of Disorders. *Ann. Int. Med.* 1 875, 1928.



The lower photomicrograph, of a lymph node, shows nodular proliferation of reticulum cells in a case of sickle cell disease with reticuloendotheliosis. The upper photomicrograph, of a section of the liver, shows engorgement of the sinusoids with sickle cells, marked proliferation of Kupffer cells and degenerative and necrotic changes in some of the liver cells in a case of sickle cell disease with reticuloendotheliosis.

and contained a number of stones, the wall was thickened. The heart, which weighed 370 Gm, was moderately enlarged. The right ventricular muscle was nearly 0.5 cm and the left 1 cm in thickness. The lungs were greatly congested, and large amounts of red, frothy fluid exuded from the cut surfaces.

The most striking observation was the tremendous enlargement of the mediastinal, tracheobronchial and abdominal lymph nodes, especially along the aorta and the gastrohepatic region. The largest measured 4 cm in diameter. The color varied from anthracotic in the tracheobronchial region to grayish brown and whitish. No caseation was observed, and no signs of tuberculous infection were seen anywhere in the body.

Microscopic preparations of the lymph nodes showed a marked increase in the reticular tissue, which was responsible for their enlargement. Numerous nodules, which were well defined and composed of proliferating reticular cells, formed the chief components of the lymphatic glands. They were of varying sizes and consisted of large, light cells rich in acidophilic protoplasm and interlacing with each other by fine protoplasmic processes and filaments. The small blood vessels were engorged with sickled cells, and blood pigment was deposited around some of the vessels. Sickled cells were also found in the meshes of the reticulum, and phagocytosis could be seen in various areas. In some lymph glands hyalinization and sclerosis replaced the reticulum nodules.

The small vessels of the liver were engorged with sickled cells. There was marked proliferation of Kupffer's cells, and phagocytosis and signs of alteration of the liver cells were observed in some areas. Some liver cells were detached from the liver cell cords and showed vacuolation and atrophy. Large amounts of blood pigment were present.

The other organs showed the characteristic microscopic picture of sickle cell anemia.

*Comment*—The first impression after postmortem examination in this case was that the condition was atypical tuberculosis. It was somewhat supported by the observation of occasional giant cells among the proliferating reticuloendothelial cells but was disproved by the absence of tubercles and the negative results of guinea pig inoculation. The obvious diagnosis, therefore, was reticuloendotheliosis of a prevalently reticular type. I agree with Jaffe<sup>15b</sup> that this condition is not characteristic of any particular infection but merely indicates abnormal irritability of the reticuloendothelial system, either acquired or congenital. The hyperplasia of the involved cells may be either nodular or diffuse.

The picture in this case was merely the characteristic one of sickle cell anemia exaggerated to an extreme degree. Jaffe<sup>15b</sup> mentioned that the Kupffer cells in the liver and the reticuloendothelial cells of the para-aortic and abdominal lymph nodes are engorged with disfigured erythrocytes in cases of sickle cell anemia, and my own observations confirm this statement. A more or less generalized enlargement of the lymph nodes has also been observed by Mason,<sup>1</sup> Dale<sup>24</sup> and Johnson and Townsend.<sup>20</sup> Enlarged mesenteric lymph nodes may frequently be observed at operation or at autopsy, and it therefore seems justifiable to consider the

reticuloendotheliosis present in this case as an unusual consequence of the sickle cell disease and as representative of a special variety of this rare syndrome of varied causation

It should be noted that giant cells of the foreign body variety have been described by Diggs<sup>15a</sup> as present in the spleen in sickle cell anemia and are common in cases of reticuloendotheliosis, as in this case

A case of typical polycythaemia vera combined with the sickle cell trait<sup>25</sup> may also be cited

CASE 2—A 45 year old Negroess showed a characteristic dusky red appearance of the mucous membranes. The spleen was slightly enlarged. Examination of the blood showed 8,250,000 red cells and 6,500 white cells per cubic millimeter. The value for hemoglobin was 145 per cent (21 Gm.), and the hematocrit value was 75. The blood volume was markedly increased, and 50 per cent of the red corpuscles were found to be sickling in the sealed preparation.

*Comment*—It should be emphasized that this particular case represents true erythremia, as contrasted with the slight erythrocytosis observed by Wintrobe and his associates<sup>28</sup> in certain cases of "compensated" Cooley's disease

It is interesting to observe that the constitutional sickle cell trait can be associated with polycythemia. I hesitate, however, to postulate that polycythemia might be induced by an exaggerated regenerative reaction of the bone marrow due to sickle cell disease, particularly since no indication of previous excessive destruction of red cells was found. This case also shows that sicklemia need not produce deleterious consequences even in the presence of polycythemia, which might be expected to increase the predisposition to thrombosis

#### THERAPEUTIC CONSIDERATIONS

The concept of the pathologic physiology of sickle cell disease advanced in this paper clearly requires institution of certain preventive measures and maintenance of a certain therapeutic point of view. If these precautions are disregarded, the consequences of the sickle cell trait may be of important and even fatal significance

It is clear that splenectomy is of no practical value in the management of the disease. This opinion is commonly accepted by all authorities today. As Diggs<sup>15a</sup> expressed it, if the patients are left alone, they will "in effect splenectomize themselves without the benefit of surgery." Iron therapy rather than liver extracts would seem to be indicated for combating the anemia, and blood transfusions are commonly used

The anemia, however, is not the most important consideration. The circulatory stasis due to engorgement of the small blood vessels by the disfigured red cells is the primary cause not only of the anemia but of

the clinical symptoms of the disease. Furthermore, it is its most serious manifestation. It is the factor responsible for the surgical risk and for what may be termed the biologic risk with such persons.

It seems logical, therefore, that all available measures to counteract circulatory stasis should be applied. Sufficient muscular exercise, massage and avoidance of unnecessarily prolonged rest in bed in accidental illnesses are of prophylactic value. Cool baths or douches may be useful in dilating the blood vessels of the internal organs by constriction of the peripheral vessels, and hot enemas may bring about dilatation of the abdominal blood vessels. Saline and dextrose infusions and blood transfusions may help to prevent circulatory stagnation. Fluids should be forced. Thyroid medication, which is a valuable method of increasing the circulatory velocity, should be part of the preparation for operation under certain circumstances. Oxygen inhalations may be beneficial in counteracting local anoxemia and therefore in inhibiting sickling of the red cells. Such measures are all theoretically sound, but their practical value can be determined only by extensive experience with them.

One prophylactic measure, however, can and should be applied routinely. All Negro patients in both medical and surgical services should be tested routinely for sickle cell anemia. By this method sickle cell disease could be differentiated from such pathologic conditions (with which it is frequently confused) as rheumatic fever, rheumatic heart disease, polyarthritis, osteomyelitis, typhoid fever and other infectious diseases, cerebral disease, peptic ulcer, appendicitis and cholecystitis<sup>2a</sup>. It is particularly important that patients in surgical services should be so tested and that a positive result be regarded as calling for a revision of the indications for the proposed operation. Surgical treatment should not be given until the measures outlined have been instituted and carried out.

My own feeling is that routine testing of the blood of Negro patients for sickling would save some lives which are now being lost because this simple precaution is omitted. In that respect it is perhaps more valuable than many other laboratory tests which are far more complicated and time consuming and which are being used indiscriminately and without special indications.

#### SUMMARY

The sickle cell trait (sickle cell anemia) is an inborn and constitutional abnormality of the erythrocytes which is encountered almost exclusively in the Negro race.

Only a few of the persons affected with this trait have sickle cell anemia. Persons suffering from sickle cell anemia are often placed in jeopardy if they have various intercurrent diseases. Surgical procedures also introduce a serious element of risk.

Unexpected deaths after operation are sometimes demonstrated at necropsy to have been caused by sickle cell anemia, which frequently was not diagnosed because it was not suspected and therefore was not searched for

Anemia is only one consequence of the sickle cell trait and, as a rule, is not its most dangerous consequence. Circulatory stasis in the small blood vessels of the internal organs is the primary and the most disastrous consequence of sickle cell anemia. Such stasis may be enhanced by surgical procedures. Sickle cell disease would therefore be a more logical term for this condition than sickle cell anemia.

The anemia associated with the disease, as well as other symptoms and signs, can be explained as a consequence of circulatory stasis due to mechanical obstruction of the blood vessels by the disfigured, elongated erythrocytes.

Parenchymal lesions of the liver may occur in association with sickle cell disease.

Cases of sickle cell disease presenting unusual clinical and pathologic pictures are reported, including a case of massive bilateral cortical necrosis of the kidney, a case of reticuloendotheliosis and a case of polycythemia vera in which the sickle cell trait was apparent.

The concept of sickle cell disease presented leads logically to special prophylactic and therapeutic considerations.



# RESPONSE OF PLASMA PROTHROMBIN TO VITAMIN K SUBSTITUTE THERAPY IN CASES OF HEPATIC DISEASE

J GARROTT ALLEN, M D

AND

ORMAND C JULIAN, M D

CHICAGO

Considerable experimental and clinical data now at hand implicate the liver as the site of prothrombin formation<sup>1</sup> Prothrombin deficiency has been reported as occurring in human subjects suffering from damage to the liver even though no biliary obstruction or fistula was present<sup>2</sup> Wilson<sup>3</sup> reported that in disease of the liver the degree of hypoprothrombinemia was directly proportional to the amount of hepatic damage as indicated by the hippuric acid test

The data presented here are concerned with prothrombin studies made on 12 patients with various types of disease of the liver and a lowered level of plasma prothrombin The initial value for prothrombin, the values after three days, one week and two weeks of treatment and the diagnosis in each case are presented in the table The prothrombin determinations were made by a modified one stage procedure described elsewhere<sup>4</sup> Each patient received 8 mg of 2-methyl-1, 4-naphthoquinone daily by mouth, accompanied with bile salts

In the cases reported here there was either a complete failure of response to the naphthoquinone (cases 1 to 10) or a delayed rise of

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From the Department of Surgery of the University of Chicago

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1 Warner, E D Plasma Prothrombin Effect of Partial Hepatectomy, *J Exper Med* **68** 831 (Dec.) 1938 Warren, R, and Rhoads, J E The Hepatic Origin of the Plasma Prothrombin, *Am J M Sc.* **198** 193 (Aug.) 1939 Pohle, F J, and Stewart, J K Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, *J Clin Investigation* **19** 365 (March) 1940

2 Kark, R, and Lozner, E L Nutritional Deficiency of Vitamin K in Man, *Lancet* **2** 1162 (Dec. 2) 1939

3 Wilson, S J Quantitative Prothrombin and Hypuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, *Proc Soc. Exper Biol & Med* **41** 559-561 (June) 1939

4 Allen, J G, Julian O C., and Dragstedt, L R. Use of Serial Dilutions in Determination of Prothrombin by the One Stage Technic *Arch Surg* **41** 873 (Oct.) 1941

prothrombin (cases 11 and 12) This is strikingly different from the reaction seen in patients with hypoprothrombinemia due to obstructive jaundice, in whom the prothrombin response to similar doses of naphthoquinone and bile salts was very rapid Without exception the value reached normal within twenty-four to thirty-six hours after initiation of

*Prothrombin Response to 2-Methyl-1, 4-Naphthoquinone in Cases of Disease of the Liver*

Case Number	Diagnosis	Prothrombin, Per Cent				Daily Dose of Naphthoquinone, Mg	Comment
		Initial	3 days After Treatment	1 Week After Treatment	2 Weeks After Treatment		
1	Alcoholic cirrhosis	48	48	48	43	8	Icterus
2	Alcoholic cirrhosis	23	25	20		8	Marked icterus, died on 7th day, diagnosis confirmed at autopsy
3	Alcoholic cirrhosis	22	22	20		8	Marked icterus died on 8th day
4	Alcoholic cirrhosis	35	33	30	26	8	Slight icterus, died on 15th day
5	Cardiac cirrhosis	43	37	53	55	8	Marked icterus, died on 23d day
6	Wilson's disease	78	64	61	63	8	No icterus
7	Fatty infiltration with peritonitis	46	43	48	40	8	Slight icterus, died on 33d day
8	Multiple abscesses of liver	57	56	54		8	Marked icterus, died on 7th day
9	Acute yellow atrophy	10	15			8	Marked icterus, hemorrhagic diathesis, died on 4th day
10	Acute yellow atrophy	48	34	50		8	Marked icterus, died on 7th day
11	Acute hepatitis	41	68	95		8	Marked icterus
12	Metastatic carcinoma	57	62	100	100	8	No icterus

therapy, even though in some instances the obstruction had been present unremittingly for several months<sup>5</sup>

It will be seen that patients with chronic disease of the liver showed the most marked failure to respond to therapy This, we believe, offers a characteristic of valuable diagnostic importance, in that failure of

<sup>5</sup> Allen, J G, and Julian, O C Clinical Use of a Synthetic Substance Resembling Vitamin K (2-Methyl-1, 4-Naphthoquinone), Arch Surg 40 912 (May) 1940

prothrombin response to adequate vitamin K therapy in cases of jaundice would imply intrahepatic disease rather than obstruction of the bile ducts as the cause of the jaundice

#### SUMMARY

The rate and amount of rise in plasma prothrombin in 12 patients with proved disease of the liver given adequate vitamin K (2-methyl-1, 4-naphthoquinone) therapy are reported. The prothrombin response in these patients is contrasted with that seen in cases of hypoprothrombinemia due to bile duct obstruction or fistula, previously reported. It is suggested that the striking difference noted is of diagnostic significance.

# TIME REQUIRED FOR BLOOD TO FLOW FROM THE ARM AND FROM THE FOOT OF MAN TO THE CAROTID SINUSES

I EFFECT OF TEMPERATURE, EXERCISE, INCREASED INTRAMUSCULAR  
TENSION, ELEVATION OF LIMBS AND SYMPATHECTOMY

LUCIAN A SMITH, MD

Fellow in Medicine, the Mayo Foundation

EDGAR V ALLEN, MD

AND

WINCHELL McK CRAIG, MD

ROCHESTER, MINN

No attempt has been made to review the literature on circulation time completely for this presentation. Extensive references may be found elsewhere<sup>1</sup>. All methods depend on determination of the time elapsing between intravascular injection of a substance and its arrival at another part of the body. This arrival may be determined objectively<sup>2</sup>.

From the Division of Medicine (Drs Allen and Smith) and the Section on Neurologic Surgery (Dr Craig), the Mayo Clinic

Abridgment of part of a thesis submitted by Dr Smith to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine

1 (a) Smith, L A. The Postoperative Arm-to-Carotid Sinus and Foot to Carotid Sinus Circulation Time in Man, with Special Reference to Effect of the Administration of Extract of Thyroid Gland, Thesis, University of Minnesota Graduate School, 1939. (b) Kvale, W F, and Allen, E V. The Rate of the Circulation in the Arteries and Veins of Man. I. Studies of Normal Subjects and of Those with Occlusive Arterial Disease and Hyperthyroidism, *Am Heart J* **18** 519, 1939. (c) Kvale, W F, Allen, E V, and Adson, A W. The Rate of the Circulation in the Arteries and Veins of Man. II. Studies of Hypertension, of Orthostatic Hypotension and of the Effects of Sympathectomy, *ibid* **18** 537, 1939. (d) Kvale, W F, and Allen, E V. The Rate of the Circulation in the Arteries and Veins of Man. III. The Influence of Temperature of the Skin, Digestion, Posture, and Exercise, *ibid* **18** 546, 1939. (e) An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow, *ibid* **18** 557, 1939.

2 (a) Koch, E, cited by Tarr, Oppenheimer, and Sager<sup>3</sup>. (b) Blumgart H L, and Yens, O C. Studies on the Velocity of Blood Flow. I. The Method Utilized, *J Clin Investigation* **4** 1, 1927. (c) Thompson, W O, Alper, J M, and Thompson, P K. The Effect of Posture upon the Velocity of Blood Flow in Man, *ibid* **5** 605, 1928. (d) Hamilton, W F, Moore, J W, Kinsman, J M, and Spurling, R G. Simultaneous Determination of the Pulmonary and Systemic

(Footnote continued on next page)

or subjectively<sup>3</sup> Loevenhart and his associates<sup>4</sup> noted marked respiratory stimulation in animals and man following intravenous injection of a solution of sodium cyanide and proposed the use of sodium cyanide

Circulation Times in Man and of a Figure Related to the Cardiac Output, *Am J Physiol* **84** 338, 1928 (e) Kinsman, J M, Moore, J W, and Hamilton, W F Studies on the Circulation I Injection Method, Physical and Mathematical Considerations, *ibid* **89** 322, 1929 (f) Klein, O, and Heinemann, J Zur Messung der Strömungsgeschwindigkeit des Blutes beim Menschen, *Zentralbl f inn Med* **50** 490, 1929 (g) Wollheim, E, and Lange, K Die Kreislaufzeit und ihre Beziehung zu anderen Kreislaufsgrößen, *Verhandl d. deutsch Gesellsch f inn Med.* **43** 134, 1931 (h) Bartels, E C, and Powelson, M H The Rate of the Circulation of the Blood in Vascular Diseases as Determined by the Use of Histamine, *Proc. Staff Meet., Mayo Clin* **4** 217, 1929 (i) Weiss, S, Robb, G P, and Blumgart, H L The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *Am. Heart J* **4** 664, 1929 (j) Robb, G P, and Weiss, S A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *ibid* **8** 650, 1933 (k) Hitzig, W M Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, *Proc Soc Exper Biol & Med* **31** 935, 1934 (l) Hitzig, W M The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, *Am Heart J* **10** 1080, 1935 (m) Candel, S Determination of the Normal Circulation Time from the Antecubital Veins to the Pulmonary Capillaries by a New Technic, *Ann Int. Med* **12** 236, 1938 (n) Blumgart, H L The Velocity of Blood Flow in Health and Disease The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, *Medicine* **10** 1, 1931 Footnote 1

3 (a) Hirschsohn, J, and Maendl, H Notiz zur Kenntnis der Hämodynamik beim Pneumothorax, *Beitr z Klin d Tuberk.* **49** 64, 1921 (b) Kahler, H Ueber Veränderungen der Blutumlaufzeit (ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien Arch f inn. Med* **19** 1, 1929 (c) Leschke, E Kreislaufzeit und Blutgeschwindigkeit, *München med. Wchnschr* **78** 2117, 1931 (d) Berinskaya, A N, and Meerzon, T I Determination of Velocity of Circulation in Functional Diagnosis of Circulation, *Klin med.* **13** 1, 1935, abstracted, *J A M A.* **104** 1680 (May 4) 1935 (e) Goldberg, S J Use of Calcium Gluconate as Circulation Time Test, *Am J M Sc.* **192** 36, 1936 (f) Spier, L C., Wright, I S, and Saylor, L A New Method for Determining the Circulation Time Throughout the Vascular System, *Am. Heart J* **12** 511, 1936 (g) Katz, G Zur Methodik der Bestimmung der Kreislaufzeit, *München med Wchnschr* **2** 2048, 1932 (h) Neubauer, E, cited by Tarr, Oppenheimer and Sager<sup>3j</sup> (i) Winternitz, M, Deutsch, J, and Brüll, Z Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion, *Med Klin* **28** 831, 1932 (j) Tarr, L, Oppenheimer, B S, and Sager, R. V The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am Heart J* **8** 766, 1933 (k) Fishberg, A M, Hitzig, W H, and King, F H Measurement of the Circulation Time with Saccharin, *Proc. Soc Exper Biol & Med* **30** 651, 1933 (l) Zwillinger, L. Ueber die Magnesiumwirkung auf das Herz, *Klin Wchnschr* **14** 1429, 1935 Koch<sup>2a</sup> Hitzig<sup>2l</sup>

4 Loevenhart, A S, Lorenz, W F, Martin, H G, and Malone, J Y Stimulation of the Respiration by Sodium Cyanid and Its Clinical Application, *Arch Int Med.* **21** 109 (Jan) 1918 Loevenhart, A S Schlomovitz, B H, and Seybold C G The Determination of the Circulation Time in Animals and Man *J Pharmacol & Exper Therap* **15** 246 1920

for the determination of circulation time in man Robb and Weiss, however, carried out the first clinical study Since then there have been several reports <sup>5</sup>

The principal site of action of the cyanide radical has been demonstrated by Heymans and his associates <sup>6</sup> to be the carotid bodies Winder and his associates <sup>7</sup> confirmed this effect on the carotid reflex mechanism by direct injection into the carotid artery in dogs After denervation of both sinuses, with or without double vagotomy, they found that twenty-five to seventy-five times the minimal effective dose of cyanide preceding denervation was required to produce respiratory effects after intravenous injection A large amount of cyanide (twenty-two times the dose injected directly into the carotid artery) was required to stimulate respiration after injection into the vertebral artery Direct injections of sodium cyanide into the fourth ventricle produced respiratory response, but the drug was definitely less effective than when injected into the carotid artery

#### METHODS USED IN PRESENT STUDY

*Sodium Cyanide Test*—The sodium cyanide method for determination of circulation time from the arm or the foot to the carotid sinus was used in this study All determinations were made only after the subject had remained supine for twenty minutes or more and after his pulse rate and blood pressure had become constant For determination of the circulation time from the arm to the carotid sinus a 2 per cent solution of sodium cyanide by weight was injected into the median

5 (a) Kissin, M, and Bierman, W Influence of Hyperpyrexia on Velocity of Blood Flow, *Proc Soc Exper Biol & Med* **30** 527, 1933 (b) Kopp, I The Arm-to-Carotid Circulation Time in Prolonged Therapeutic Fever, *Am Heart J* **11** 667, 1936 (c) Ellis, L B Circulatory Adjustments to Moderate Exercise in Normal Individuals, with Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, *Am J Physiol* **101** 494, 1932 (d) Cohen, M E, and Thomson, K J Studies on the Circulation in Pregnancy I The Velocity of Blood Flow and Related Aspects of the Circulation in Normal Pregnant Women, *J Clin Investigation* **15** 607, 1936 (e) Robb, G P, and Weiss, S The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Diseases Their Relation to Clinical Types of Circulatory Failure, *Am Heart J* **9** 742, 1934 (f) McGuire, J, and Goldman, F Apparent Increased Velocity of Blood Flow in Cases of Congenital Heart Disease with Septal Defects Having Right-to-Left Shunt, *ibid* **14** 230, 1937 (g) Youmans, J B, Akeroyd, J H, Jr, and Frank, H Changes in the Blood and Circulation with Changes in Posture The Effect of Exercise and Vaso-dilatation, *J Clin Investigation* **14** 739, 1935

6 Heymans, C, Bouckaert, J J, and Dautrebande, L Sinus carotidien et réflexes respiratoires III Sensibilité des sinus carotidiens aux substances chimiques Action stimulante respiratoire réflexe du sulfure de sodium, du cyanure de potassium, de la nicotine et de la lobéline, *Arch internat de pharmacodyn. et de thérap* **40** 54, 1931

7 Winder, C V, Winder, H O, and Gesell, R The Seat of Action of Cyanide on Pulmonary Ventilation, *Am J Physiol* **105** 311, 1933

antecubital vein (vena mediana cubiti) The amount used was approximately 0.11 mg for each kilogram of body weight. The level of the vein was approximately the same as that of the right auricle when injections were made, that is, the patient was supine. The needle (20 gage) was held in the vein for at least thirty seconds, so that normal venous blood flow might be established after release of the tourniquet. A stop watch was used to measure the time elapsing between the start of the rapid injection and the end point reaction. The time of injection for the arm was about one second, and that for the foot, about two seconds. Because the first reaction was a rapid dilation of the alae of the nose, followed quickly by a sharp inspiratory gasp and tachypnea, dilation of the alae was used as the end point. Approximately twice the size of the effective arm dose of sodium cyanide, or 0.22 mg per kilogram of body weight, was needed for determination of the circulation time from the foot to the carotid sinus. If the response to injection into the median antecubital vein had been too vigorous, 1 mg was subtracted from the quantity of sodium cyanide to be injected into the vein in the foot, if the reaction had been too weak, 1 mg was added to it. Allowing an interval of ten minutes to elapse before repeating the dose of sodium cyanide was found to be a necessary precaution. Venipuncture in the foot was most convenient in the large vein anterior to the internal malleolus. A 24 gage needle was used for venipunctures in the foot, which also were performed with the vein at the approximate level of the right auricle. Because unforeseen reactions are possible when sodium cyanide is used, antidotes, including ampules of amyl nitrite, 10 per cent solution of sodium thiosulfate and a solution of methythionine chloride (methylene blue), were kept at hand, and epinephrine hydrochloride was kept ready in a syringe.<sup>8</sup>

In our tests of circulation time we considered that the interval between injection of sodium cyanide and dilation of the alae of the nose represented the circulation time from the point of injection to the carotid sinus. Objections to this assumption were considered by Kvale, Allen and Adson<sup>10</sup>. We wish to emphasize also that when circulation time is decreased the blood flows faster. The reverse is also true.

The greatest advantages of using sodium cyanide are that the response is objective and that the volume of solution to be injected is small, a distinct advantage for venipunctures in the foot. One of the greatest objections is that the persons studied often dislike the sensation of air hunger produced by the respiratory stimulation. In about 600 injections of sodium cyanide, localized venous thrombosis occurred 8 times. General systemic reactions occurred 8 times, 5 reactions were moderate, and 3 were severe. Intravenous injection of the drug is not entirely safe. We favor use of the solution of calcium and magnesium described elsewhere.<sup>9</sup>

*Intramuscular Tension*—The method used for determination of intramuscular tension was essentially that described by Henderson, Oughterson, Greenberg and Searle,<sup>10</sup> except for minor modifications. In this procedure an attempt is made to measure the intramuscular pressure exerted by involuntary tone of voluntarily relaxed muscle. This is done by determining the amount of pressure,

8 Hanzlik, P. J., and Richardson, A. P. Cyanide Antidotes, J. A. M. A. 102:1740 (May 26) 1934.

9 Kvale, Allen and Adson<sup>10</sup>. Kvale and Allen<sup>11</sup>.

10 Henderson, Y., Oughterson, A. W., Greenberg, L. A., and Searle, C. P. Muscle Tonus, Intramuscular Pressure and the Venopressor Mechanism, Am. J. Physiol. 114:261, 1936.

measured by a water manometer, required to force physiologic solution of sodium chloride into the belly of the muscle tested. To a specially prepared 20 gage needle with a solder-filled tip and several lateral holes is attached a glass connector with a narrow lumen. These are filled with physiologic solution of sodium chloride, which makes a meniscus in the lumen of the glass connector. The needle then is inserted into the muscle through a wheal raised by the injection of procaine hydrochloride into the skin, and a U tube water manometer is attached to the glass connector by rubber tubing. The height of the column of water required to force the meniscus downward is determined and represents what is probably intramuscular tension in terms of millimeters of water. After each test the meniscus returned to its original pressure as a result of decrease of the pressure in the water manometer. Repeated determinations did not significantly influence the readings. We are not concerned in this paper with objections that muscular tone cannot be studied in this way.

TABLE 1—*Circulation Time in Normal Subjects*

Time, Seconds	Number of Tests	
	Arm to Carotid Sinus	Foot to Carotid Sinus
10-14	7	0
15-19	29	0
20-24	34	2
25-29	13	12
30-34	3	15
35-39	0	12
40-44	0	16
45-49	0	12
50-54	0	5
55-59	0	2
60-64	0	0
65-70	0	1
Total	86	77
Average	20.1	38.7

The study of normal subjects was made in all instances on persons who had no demonstrable fault in their circulatory systems. These were chosen from among physicians, technicians and ambulatory patients, some of whom were studied before operation.

#### RESULTS OF STUDY OF NORMAL PERSONS

The average circulation time from the arm to the carotid sinus for 86 normal persons was twenty and one-tenth seconds, with a range of twelve and four-tenths to thirty-three and two-tenths seconds, although only 3 had a circulation time of thirty or more seconds (table 1). When the circulation time from the arm to the carotid sinus seemed too great for normal subjects, the test was usually repeated, and almost invariably the results were approximately the same. The explanation why the average arm to carotid sinus circulation time as determined in this study was greater than the average values found by others is not easy.<sup>11</sup> Sev-

11 Gargill, S. L. The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.* 209:1089, 1933. Wood, P. Right and Left Ventricular Failure. A Study of Circulation Time and Venous Blood Pressure, *Lancet* 2:15, 1936. Robb and Weiss.<sup>21</sup> Kopp.<sup>5b</sup>



eral factors influence circulation time, and, since the conditions of our test were not identical with those used by other investigators, it is not surprising that the results are not the same. Since there are many physiologic variations, it is well to consider that there is no normal circulation time but only a normal circulation time under a specific set of conditions. In our studies, results were discarded when the end reactions were not sharp. Determination of the foot to carotid sinus circulation time in 77 instances revealed that an average of thirty-eight and seven-tenths seconds was required. The range of values was from twenty-two to sixty-seven seconds (table 1).

TABLE 2—*Effect of the Temperature of an Extremity on Circulation Time*

Study No	Extremity	Surface Temperature of Fingers or Toes, C	Circulation Time, Seconds	Pulse Rate, Beats per Minute	Oral Temperature, F	Respirations per Minute	Blood Pressure, Mm of Mercury	Conditions of Study
1	Right arm	31.0	25.0	60	97.4	14	84/54	Control
	Right arm	30.1	27.4					
	Right foot	23.6	37.2					
	Right arm	34.6	21.8	60	97.2	14	86/54	After reflex vasodilatation by heat over the trunk
	Right foot	32.6	24.0					
2	Left arm	25.6	28.6	54	97.8	14	84/56	Control
	Left foot	23.6	37.8					
	Left arm	33.0	22.2	60	97.7	14	86/56	After reflex vasodilatation by heat over the trunk
	Left foot	33.2	23.2					
3	Right arm	24.2	36.8	54	97.2	14	88/56	Control
	Right foot	20.7	49.4					
	Right arm	33.2	25.8	56	96.5	14	84/56	Vasodilatation by 2 ounces (60 cc) of ethyl alcohol
	Right foot	32.6	25.4					
4	Left arm	17.8	29.2	50	97	14	104/56	Control
	Left foot	17.5	60.8					
	Left arm	35.2	18.6	64	97.1	16	94/62	Vasodilatation by heat tent over legs
	Left foot	35.6	19.8					

#### CIRCULATION TIME AFTER CHANGES IN THE TEMPERATURE OF THE SKIN

A cooperative, phlegmatic, normal young man who was accustomed to laboratory procedures was the subject of this study, which was carried out in a room in which the air was maintained at constant temperature and humidity. He rested in bed until the temperature of the skin of his exposed extremities was constant. After control determinations of circulation time had been made, vasodilatation was induced reflexly by placing over the trunk a baker, the air in which was at a temperature of 55 to 60 C. This study was repeated, and on other occasions vasodilatation was induced by administration of 2 ounces (60 cc) of ethyl alcohol and by direct application of heat to the legs. The pulse rate,

blood pressure, oral temperature and respiratory rate did not change significantly. Increase in the temperature of the skin was associated with decreased circulation time (table 2). Moreover, when the skin was warm the respiratory responses were more vigorous than when it was cold, although identical amounts of the drug were injected.

These studies appear to indicate that blood in veins flows faster when the skin is warm than when it is cold. This observation was confirmed by the studies of Kvale and his associates<sup>9</sup> on the circulation time in arteries. It is probable that the temperature of the skin is one of the most important regulators of speed of blood flow in the veins of the limbs. During vasodilatation the circulation time decreased from the arm and from the foot to the carotid sinus, this was effected by an increased volume flow of blood resulting from relaxation of arterioles or from opening of arteriovenous shunts. Veins do not appear to relax or dilate in the same degree, for, if they did, it appears probable that

TABLE 3—*Effect of Exercise on Circulation Time*

Case	Arm to Carotid Sinus Circulation Time, Seconds			Foot to Carotid Sinus Circulation Time, Seconds		
	Before Exercise	After Exercise	Increase or Decrease	Before Exercise	After Exercise	Decrease
1	23.6	23.6	0	49.8	32.2	17.6
	16.0	16.8	+2.8	53.6	40.6	13.0
2	20.8	23.8	+3.0	46.4	33.2	13.2
3	17.8	19.6	+1.8	42.8	33.4	9.4

the blood would not flow faster in them when the arterioles are dilated. It seems logical to assume that if reflex dilation of veins were parallel in magnitude to that of arterioles, there should be no resultant change of circulation time from an extremity to the carotid sinus.

#### CIRCULATION TIME AFTER ACTIVE EXERCISE OF AN EXTREMITY

Three subjects whose ages ranged from 29 to 50 years were chosen for the tests. Preliminary determinations were made after rest in bed for forty-five to sixty-five minutes. A standard form of exercise was performed with the subject in the supine position to eliminate the influence of posture. The pulse rate was not influenced significantly by this type of exercise. Exercise of the arms consisted of moving the extended arm up and back of the head about forty times per minute and at the same time rapidly gripping the fingers into a fist and then extending them. This was continued for two minutes. The circulation time of the blood from the arm to the carotid sinus was determined within one minute after cessation of exercise. Exercise of the legs consisted of alternately lifting and dropping the leg to be tested about forty times.

minute and wiggling the foot vigorously at the same time. The tests of circulation time were performed within two minutes of cessation of exercise.

The results obtained are presented in table 3. A decrease of the circulation time from the foot to the carotid sinus occurred uniformly after exercise of the legs and varied from 24 to 40 per cent. The decrease in the circulation time from the foot to the carotid sinus as a result of exercise seems related to vasodilation, which occurs in muscle as a result of exercise.<sup>12</sup> The response after exercise of the arms was in contrast to this, the circulation time from the arms to the carotid sinus remained the same in 1 case and actually increased in 3. We have no adequate evidence to explain why the circulation time from the arm to the carotid sinus did not change in the same direction as that from the foot to the carotid sinus as a result of exercise. We can only assume that other factors tending to increase circulation time from the arm to the carotid sinus were not overcome by exercise of the hand and arm. Cutaneous vasoconstriction induced by elevation and exercise of the arm may have been one factor.

#### CIRCULATION TIME DURING ELEVATION OF AN EXTREMITY

The circulation time of 4 persons was studied. Control values were obtained after thirty to sixty minutes of rest in bed. The temperatures of the room were not controlled, but no drafts were allowed, and the lapse of time in each experiment was brief, so that the room temperature was relatively constant. With the median antecubital vein at the level of the right auricle, the circulation time from the arm to the carotid sinus was determined. The same dose of sodium cyanide was repeated eight to ten minutes later, the needle for injection was reinserted into the vein, and thirty seconds after removal of the tourniquet the arm, with the needle still in place, was elevated to an angle of about 70 degrees. Injection then was done as before. Ten minutes after a control test of the circulation time from the foot to the carotid sinus, a needle was inserted into the same vein used previously. The heel was then placed on a support of previously arranged blankets so that the leg was propped at an angle of about 30 degrees, and the test was repeated. The pulse rate did not change as a result of elevating the extremity.

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<sup>12</sup> Anrep, G. V. *Lance Medical Lectures. Studies in Cardiovascular Regulation*, Stanford University, Calif., Stanford University Press, 1936, vol. 3. Kaufmann, M. *Recherches experimentales sur la circulation dans les muscles en activite physiologique*, *Arch de physiol norm et path* **24**: 279, 1892. Krogh, A. *The Anatomy and Physiology of Capillaries*, ed. 2. New Haven, Conn., Yale University Press, 1929.

Results of 5 tests on the arm and on the leg are given in table 4. In all instances definite decrease of circulation time resulted from elevation of the arms and legs. This apparently was an effect of gravity.

#### CIRCULATION TIME AFTER LUMBAR SYMPATHECTOMY

Studies of circulation time were made on 9 patients after surgical treatment for hypertension. Surgical treatment in all of the cases con-

TABLE 4—*Effect of Elevation of Extremities on Circulation Time*

Case No	Arm to Carotid Sinus Circulation Time, Seconds			Foot to Carotid Sinus Circulation Time, Seconds		
	Before Elevation	After Elevation	Decrease	Before Elevation	After Elevation	Decrease
1	23.8	20.4	3.4	46.4	35.2	11.2
2	18.8	15.0	3.8	44.0	32.8	11.2
4	17.4	14.4	3.0	42.2	37.6	4.6
	17.0	14.8	2.2	39.0	36.0	3.0
5	22.8	20.0	2.8	32.8	29.8	3.0

TABLE 5—*Circulation Time Following Sympathectomy*

Case	Sympa- thectomized Side	Blood Pressure, Mm of Mercury		Pulse Rate, Beats per Minute	Circulation Time, Seconds		
		Systolic	Diastolic		Arms to Carotid Sinus	Foot to Carotid Sinus	
						Right	Left
6	Left	222	110	84	17.6	43.6	31.8
	Both	216	104	94	13.6	42.4	46.4
7	Neither	176	122	76	20.8	63.0	
	Both	166	116	86		24.8	34.6
8	Right	160	104	96	15.8	23.8	28.6
	Both	144	92	96	14.2	48.4	36.2
9	Neither	188	116	68	28.6	94.6	95.4
	Right	176	100	80	23.2	33.0	82.0
	Both	176	106	72	25.6	34.2	39.2
10	Neither	148	102	72	23.6	96.6	49.2
	Right	152	100	80	19.4	32.0	39.2
11	Neither	214	122	72	17.2	75.0	37.2
	Both	184	110	80		41.0	27.4
12	Right	210	120	84	13.6	27.0	24.0
	Both	164	108	88		35.2	52.6
13	Right	152	92	88	20.4	43.2	32.2
	Both	180	116	104	12.2	33.4	32.0
14	Left	170	118	96	20.0	41.2	39.6
	Both	136	90	84		37.8	

sisted of operation in two stages ten to fourteen days apart, in each of which unilateral lumbar sympathectomy and splanchnicectomy were performed.<sup>13</sup> The postoperative studies were done seven to thirteen days after operation. The results obtained from determinations of circulation time made preoperatively in some cases and postoperatively

13 Adson, A. W., Craig, W. McK., and Brown, G. E. *Surgery in Its Relation to Hypertension*, Surg., Gynec. & Obst. **62**: 314, 1936. Allen, E. V., and Adson, A. W. *The Physiological Effects of Extensive Sympathectomy for Essential Hypertension*, Am. Heart J. **14**: 415, 1937.

in all are given in table 5. These demonstrate conclusively that lumbar sympathectomy causes a decrease in the circulation time from the foot to the carotid sinus, for in every instance in which the circulation time was determined from both feet to the carotid sinuses after unilateral sympathectomy it had decreased on the side affected by the sympathectomy (table 5). The effect of sympathectomy on circulation time is similar to that of vasodilatation, and the explanation for this seems to be the same. The temperature of the skin of the feet increased as a result of sympathectomy.

Two other observations are of interest. After both operations had been performed, the circulation time from the foot to the carotid sinus was greater on the originally sympathectomized side than it had been after the first operation and was less in the more recently sympathecto-

TABLE 6—*Intramuscular Tension and Circulation Time After Injection of Strychnine Intramuscularly*

Strychnine Amount Injected	Relation to Time of Injection	Intramuscular Tension of Biceps Muscle, Mm of Water		Circulation Time, Seconds	
		Maximum	When Circulation Time Was Redetermined	Arm to Carotid Sinus	Foot to Carotid Sinus
1/.0 grain (3 mg)	Before	33		21	63
	After	122	105	25	52
1/15 grain. (4.3 mg)	Before	38		20	48
	After	113	113	22	27
1/12 grain (5.4 mg)	Before	45		16	30
	After	100	60	17	32
1/15 grain (4.3 mg)	Before	10		24	51
	After	93	40	19	47
1/10 grain (6 mg)	Before	8		22	45
	After	100	50	24	43

mized side, with 1 exception (case 9). These observations suggest to us that vascular tone in limbs to which the sympathetic fibers have been cut is regained gradually.

#### INTRAMUSCULAR TENSION AND CIRCULATION TIME

Henderson and his associates<sup>10</sup> demonstrated that intramuscular injection of strychnine produces a generalized increase in intramuscular tension and concluded that this is one way to affect venous circulation. It was desirable to know the effect of strychnine on circulation time when the intramuscular tension determined by their method was increased. Accordingly, studies were made on 5 persons. After rest in bed for thirty to sixty minutes, control determinations of intramuscular tension in one biceps muscle and of circulation time were made. While the needle for determination of intramuscular tension remained in place, strychnine, varying in amounts from 1/20 to 1/10 grain (3 to 6

mg) was injected intramuscularly into the opposite arm. The blood pressure, pulse and intramuscular tension were determined at intervals of from two to four minutes. A sharp increase in the apparent intramuscular tension began ten to fifteen minutes after the injection and increased to values approximating those obtainable by voluntary contraction of muscle. All of the 5 subjects responded to strychnine thus. The blood pressure and pulse rate were not changed significantly. At the height of the response of intramuscular tension, or as near it as was technically possible, the circulation time was determined again for the pathways from the arm and from the foot to the carotid sinus. The results are given in table 6. The circulation time from the arm to the carotid sinus was affected variably, and in only 1 instance was it decreased, but that from the foot was decreased in 4 of 5 instances. Although this decrease of circulation time was not great, it was thought to be significant because of the greatly increased magnitude of the respiratory reaction. The reactions were similar in magnitude to those which occurred when the test was performed after vasodilatation had been induced in other subjects. It was felt that the venous circulation time from the predominantly muscular lower extremities was probably decreased by the increase in intramuscular tension resulting from administration of strychnine.

#### CONCLUSIONS

1 The mean circulation time from the arm to the carotid sinus of normal persons in the present study was twenty and one-tenth seconds. The range was twelve and four-tenths to thirty-three and two-tenths seconds. The mean circulation time from the foot to the carotid sinus was thirty-eight and seven-tenths seconds. The range was twenty-two to sixty-seven seconds.

2 The temperature of the skin of the extremities has a prominent effect on circulation time from the foot to the carotid sinus and from the arm to the carotid sinus. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

3 Exercise of the legs decreases circulation time in the legs.

4 Elevation of an extremity decreases circulation time in the extremities.

5 Lumbar sympathectomy decreases circulation time in the legs.

6 The increase of intramuscular tension caused by strychnine tends to decrease circulation time in the legs.

# CIRCULATION TIME FROM FOOT TO CAROTID SINUS AND FROM ARM TO CAROTID SINUS OF MAN

## II EFFECTS OF OPERATION AND OF ADMINISTRATION OF THYROID GLAND, POSTOPERATIVE PHLEBITIS AND PULMONARY EMBOLISM

LUCIAN A SMITH, M D

Fellow in Medicine, the Mayo Foundation

AND

EDGAR V ALLEN, M D

ROCHESTER, MINN

A description of the method used and the values for circulation time obtained with normal subjects and under various physiologic conditions have been presented in another communication<sup>1</sup> The method consists of determining the time elapsing between the injection of a 2 per cent solution of sodium cyanide into an antecubital vein or into a vein of the foot and the appearance of rapid dilatation of the alae of the nose, followed by an inspiratory gasp and then by tachypnea Ordinarily 0.11 mg of sodium cyanide was injected for each kilogram of body weight when the circulation time from the arm to the carotid sinus was studied, and twice this amount was injected when the circulation time from the foot to the carotid sinus was studied However, if the respiratory response was excessive when the time from the arm to the carotid sinus was determined, 1 mg was deducted from the calculated total dose for studying the circulation time from the foot to the carotid sinus Similarly, if the respiratory response was minimal when the circulation time from the arm to the carotid sinus was determined, 1 mg was added to the calculated amount of sodium cyanide to be used for determination of the circulation time from the foot to the carotid sinus In all instances the calculated time included the time required for injection, which was performed as quickly as possible The time required was about one second for injection into a vein of the arm and about two seconds for injection into a vein of the foot The solvent was about 0.33 cc in volume

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From the Division of Medicine, the Mayo Clinic.

1 Smith, L A , Allen, E V , and Craig, W McK Time Required for Blood to Flow from the Arm and from the Foot of Man to the Carotid Sinuses I Effect of Temperature, Exercise, Increased Intramuscular Tension Elevation of Limbs and Sympathectomy, Arch. Surg. this issue pp 1366-1376

for determination of the arm to carotid sinus circulation time and about 0.67 cc for determination of the foot to carotid sinus circulation time. A vein at the cubital fossa and one over the internal malleolus were used for the respective tests. A 20 gage needle was used for the veins of the arm and a 24 gage needle for the veins of the foot. Reactions to injections have been noted previously.<sup>1</sup>

The circulation time of 31 persons was determined on the night before operations which were performed in the morning or in the morning before operations which were performed in the afternoon, the observations were repeated after operation. No attempt was made to control environmental factors, as it was desirable to study the circulation time under circumstances ordinarily present before and after operation. The 21 men and 10 women who were the basis of this study were from 31 to 68 years of age (average 48 years), of an average height of 66 inches (168 cm) and of an average weight of 147 pounds (66.7 Kg). It does not seem necessary to list individual values here. The average systolic blood pressure, measured in millimeters of mercury, was 123, and the average diastolic blood pressure was 71. The operations performed are listed in table 1. Determination of circulation time was made repeatedly in the course of ten postoperative days in 9 instances and in the course of thirteen postoperative days in 22 instances. Eight additional men (patients) were given desiccated thyroid gland by mouth after operation as part of a plan for preventing venous thrombosis and embolism. The averages for height, weight and age were 69 inches (175 cm), 169 pounds (76.7 Kg) and 50 years respectively. The operations are listed in table 2. Results of studies to determine the effects of administration of thyroid on the circulation time in cases in which operation was not performed or in which the patients were ambulatory without detectable impairment of circulation are given in table 3.

#### EFFECT OF OPERATION ON CIRCULATION TIME<sup>2</sup>

The average A-C time (table 1) determined before operation was twenty-one seconds. In the period of two to six hours after operation the A-C time decreased in 6 of the 8 cases studied (table 1). On the day following operation the A-C time was less than before operation in 2 of the cases studied (48 and 88 seconds respectively) and essentially unchanged in the other 2 cases (table 1). It is our opinion that there was a significant increase in A-C time at some time after operation in

<sup>2</sup> For the sake of convenience the following abbreviations will be used: A-C time = time elapsing between injection of sodium cyanide into a vein at the elbow and dilatation of the alae of the nose. F-C time = time elapsing between injection of sodium cyanide into a vein of the foot and dilatation of the alae of the nose.



12 of the 31 cases studied (39 per cent) The mean of the A-C circulation times is shown in chart 1

The average preoperative F-C time (table 1) was thirty-nine seconds In 5 of the 9 cases studied during the postoperative period (two to six hours), the F-C time decreased significantly<sup>3</sup> Two days after operation the average F-C time was greater than the average preoperative F-C time, and beginning on about the fifth postoperative day the average F-C time increased rather markedly (chart 2) Subsequently the average

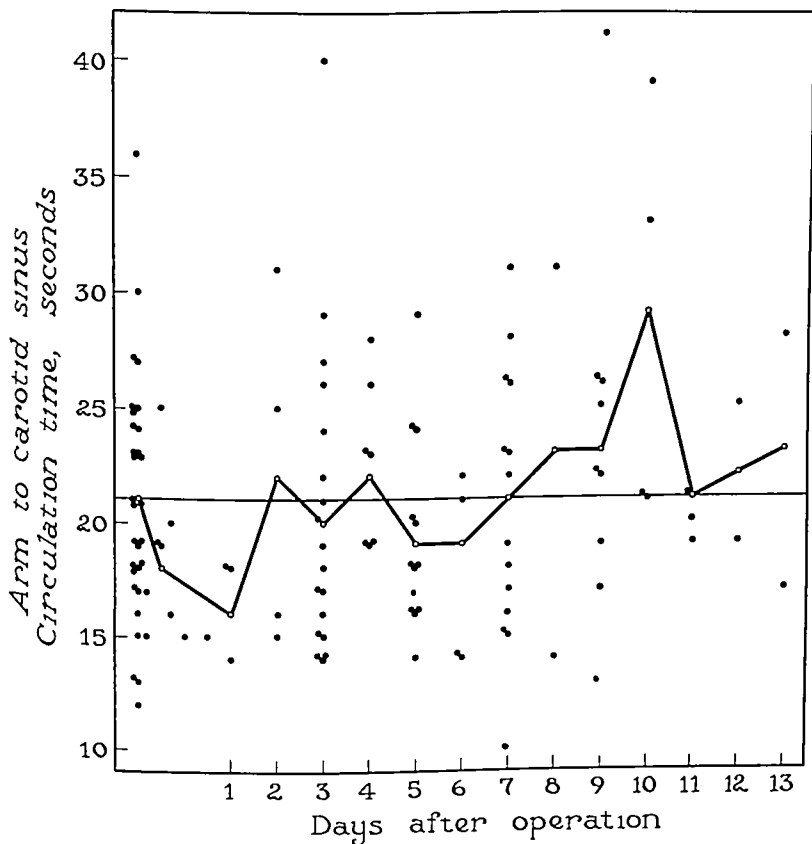


Chart 1—Circulation time from the arm to the carotid sinus The horizontal line shows the mean preoperative circulation time. The irregular line shows the mean circulation time at various periods

F-C time was always greater than before operation A study of the F-C time in individual cases, rather than the average F-C time, indicated that in 23 of 28 cases (82 per cent) the F-C time increased significantly at some time after operation (table 1)

<sup>3</sup> We consider that an increase or decrease in A-C or in F-C time of less than four seconds is insignificant

TABLE 1—Circulation Time in Cases in Which Operation Was Performed

Case	Operation	Circulation Time, Seconds	Relation to Operation												
			Days After Operation												
			1	2	3	4	5	6	7	8	9	10	11	12	13
		2 to 6 Hours After													
1	Lumbar sympathectomy *	Before	178			194									
		After	330			454									
2	Cholecystectomy *	Before	226												
		After	348												
3	Thyroidectomy,† B M R +3%	Before	190												
		After	376												
4	Excision of hydrocele and of lipoma of abdominal wall *	Before	156												
		After	524												
5	Abdominal hysterectomy *	Before	232												
		After	284												
6	Thyroidectomy,† B M R +50%	Before	178												
		After	342												
7	Abdominal exploration *†	Before	212												
		After	334												
8	Thyroidectomy,† B M R +12%	Before	248												
		After	408												
9	Thyroidectomy,† B M R +20%	Before	206												
		After	304												
10	Cholecystectomy *	Before	214												
		After	416												
11	Cholecystectomy, gastroduodenostomy *†	Before	360												
		After	712												
12	Sigmoidectomy *	Before	252												
		After	474												
13	Gastro-enterostomy *	Before	134												
		After	200												
14	Re section of colon *†	Before	212												
		After	258												
15	Re section of carcinoma of sigmoid *	Before	178												
		After	342												

16	Herniotomy excision adenomyoma *†	A O F O	23 0 47 0	21 0	21 4 60 6	21 0 70 4
17	Dilation and curettage cauterly to cervix *	A O F O	17 8 23 6	14 0	13 8	
18	Ileocolostomy *	A O F O	13 4 22 2	13 8 21 6	14 2 27 8	13 0 27 2
19	Resection of colon †	A O F O	18 0 42 0	15 2 10 2		
20	Salpingectomy appendectomy *	A O F O	19 2 28 2	24 2 27 4	16 2 23 4	17 2 33 6
21	Appendectomy removal of ovarian cyst *	A O F O	27 4 42 4	19 8	18 0	
22	Herniorrhaphy *	A O F O	26 6 64 0	20 6 78 4		39 0 83 4
23	Cholecystectomy *;	A O F O	17 2 26 0		14 4 49 0	
24	Partial gastrectomy	A O F O	24 2 46 6	20 2 30 6	20 2 44 6	25 0 39 6
25	Herniorrhaphy †	A O F O	24 2 32 8	28 8 44 8	24 2 53 0	21 0 47 4
26	Herniorrhaphy †	A O F O	19 0 48 4	18 6 33 6	20 2 52 0	23 0 67 8
27	Cholecystectomy †	A O F O	30 0 38 2	22 4 38 4	10 8 42 2	24 4 68 4
28	Cholecystectomy appendectomy *†	A O F O	18 0 31 4	14 6 41 2	18 3 55 2	25 6 50 8
29	Cholecystectomy appendectomy *;	A O F O	12 4 28 8	15 8 43 0	10 0 41 2	
30	Resection of colon *;	A O F O	17 0 41 8	17 0 38 4	16 0 28 2	30 2 40 2
31	Herniorrhaphy †	A O F O	15 0 40 8	16 8 54 8	18 2 66 0	22 2 67 4
Inhalation anaesthesia † Regional anaesthesia ‡ Spinal anaesthesia				A C arm to carotid sinus pathway F O foot to carotid sinus pathway P E pulmonary embolism		
						25 4 P E on 22d day 18 6 47 2

TABLE 2—Effect on Circulation Time of Administration of Thyroid Extract to Patients on Whom Operation Was Performed

Case	Operation	Relation to Operation																	
		Before	Days After Operation																
			2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
32	Colostomy *†	O T, seconds	24.6		21.4														
		F O	67.0		40.4														
	Thyroid, † grains					2	0	0											
					(0.13 Gm)														
										(0.26 (0.39 Gm) Gm)									
33	Abdominal exploration, carcinoma of rectum †	O T, seconds	28.2	27.8															
		F O	30.0	53.4															
	Thyroid, grains					6	0	4	0	4									
34	Appendectomy *†	O T, seconds	30.8	18.4			15.4												
		F O	44.4	52.0			30.0												
	Thyroid, grains			0	0	0	4	2											
35	Resection of ileum and half of right colon *	O T, seconds	26.0	20.0		15.0		20.2		19.2									
		F O	44.6	38.0		31.6		47.0		45.8									
	Thyroid, grains			2	2	2	4	0	0	2									
36	Colostomy and exteriorization of sigmoid †	O T, seconds	33.2	18.0		20.0		23.2		28.0									
		F O	45.2	57.4		58.0		39.0		50.2									
	Thyroid, grains			4	4	0	4	3											
37	Gastro enterostomy *	O T, seconds	18.6		20.4		13.8		15.0		24.0								
		F O	30.0		37.6		36.4		32.0		34.2								
	Thyroid, grains				6	0	0	6	0										
38	Cholecystectomy *	O T, seconds	22.4	18.0		10.8		10.0		23.6		15.4							
		F O	48.4	33.0		39.4		35.2		43.0		32.0							
	Thyroid grains				6	0	6	6	0	0	6								
39	Repair of ventral hernia †	O T, seconds	20.0	17.2		21.4		20.4		20.0		20.8		20.2				20.0	
		F O	51.0	52.8		35.4		36.0		32.4		37.0		40.4				39.0	
	Thyroid grains			4	0	0	0	0	0	0	0	0	0	4	4	0	2		

\* Inhalation anesthesia  
† Ethyl anesthesia

A O arm to carotid sinus pathway  
F O foot to carotid sinus pathway  
C I circulation time

Because the circulation time was not determined at the same time in relation to operation in all of these cases, we selected the results of study of circulation time in a second group of subjects for reconsideration because there was fair uniformity of relation of the time of the test to operation in these cases, because studies were carried out over sufficiently long periods and because major operations had been performed. In addition, we excluded instances of hyperthyroidism, which in itself might

TABLE 3—*Effect on Circulation Time of Administration of Thyroid Extract to Normal Subjects*

Case	Day	Thyroid Extract Grains	Circulation Time		Pulse Rate
			A C *	F C †	
40		0	22	35	66
	1	4			
	2	6	24	39	78
	3	6	18	37	80
	4	4	17	27	84
41	5	2	19	34	70
		0	20	40	66
	1	4			
	2	6	24	65	72
	3	6	15	60	72
42	4	4	20	39	84
	5	2	16	38	82
		0	22	42	72
	1	4			
	2	6	24	52	80
43	3	6	18	31	84
	4	6	18	32	84
	5	0	17	30	80
	6	0	22	29	84
	7	0	23	38	84
	8	0	23	36	80
	9	0	23	41	80
		0	18	35	72
	1	4			
44	2	6	21	45	84
	3	6	19	40	80
	4	6	14	29	90
	5	0	14	31	84
	6	0	21	29	88
	7	0	22	30	90
	8	0	19	28	84
	9	0	20	37	72

\* Arm to carotid sinus time in seconds

† Foot to carotid sinus time in seconds

influence circulation time, and cases of sympathectomy, which might influence the circulation time specifically. The 10 cases in this group presented characteristic examples of rather routine major surgical procedures (cases 18, 19, 23, 24, 25, 26, 27, 29, 30 and 31, table 1). The influence of operation on circulation time is illustrated strikingly in chart 3. The average A-C time remained essentially unchanged in this group until the ninth postoperative day, when it increased about five seconds from a preoperative average value of nineteen and one-tenth seconds. The F-C time increased regularly from thirty-three and three-

tenths seconds before operation to fifty-six and one-tenth seconds on the eleventh postoperative day

These studies indicate to us several interesting changes in the speed of blood flow in veins of the extremities after operation <sup>4</sup> The decreased circulation time noted shortly after operation apparently results from the vasodilating effect of anesthesia and of fever and possibly from

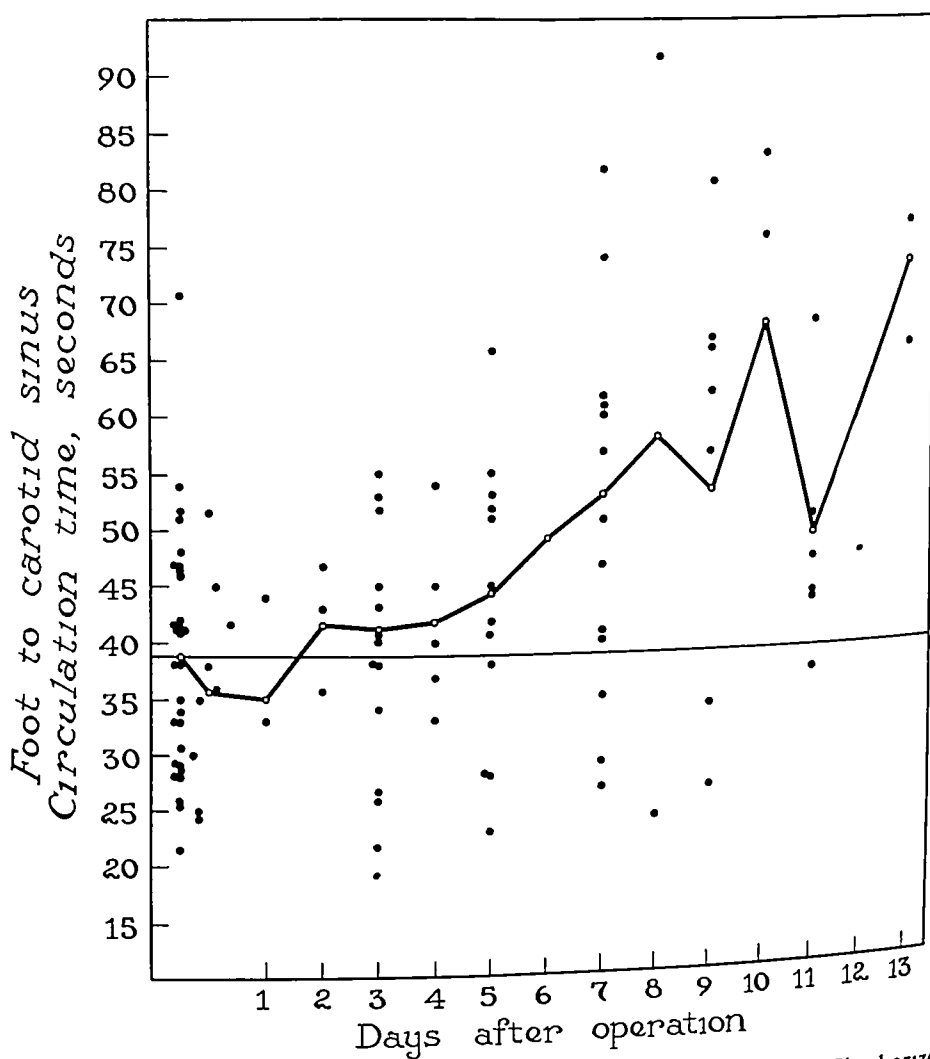


Chart 2—Circulation time from the foot to the carotid sinus The horizontal line shows the mean preoperative circulation time The irregular line shows the mean circulation time at various periods

4 We are aware that the test indicates the rate of circulation in the veins of the extremities and in the heart and pulmonary circulation We believe that changes in circulation time noted in these studies, however, are a measure of changes in rate of circulation in peripheral veins This belief is supported by the data summarized in chart 3 The A-C time changed little, and the F-C time changed much If these changes were due to changes in rate of circulation in the heart and lungs, the A-C and F-C times should have changed similarly

tachycardia The cause of increases in circulation time which occur subsequently will be considered later

#### GENERAL CONSIDERATION OF RELATIONS OF CIRCULATION TIME TO POSTOPERATIVE VENOUS THROMBOSIS AND PULMONARY EMBOLISM

From the beginning of the study it was obvious that the postoperative changes in the F-C time, which usually were marked, would be of much greater interest than the changes in the A-C time, which usually were not marked (table 1, charts 1, 2 and 3) This observation seems to have definite significance when applied to the problem of postoperative pulmonary embolism It is very rare for thrombophlebitis or venous thrombosis to occur in the veins of the arms postoperatively Conversely,

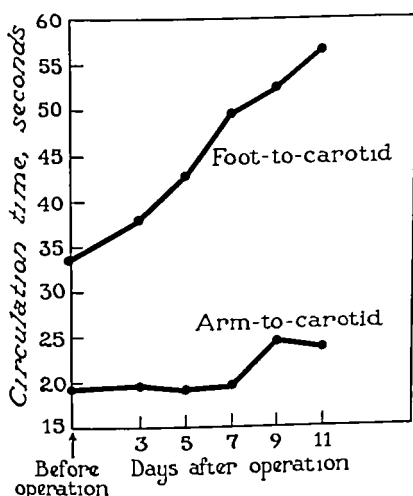


Chart 3—Circulation time from the arm to the carotid sinus and from the foot to the carotid sinus in a selected group of patients (see text)

thrombophlebitis and thrombosis leading to embolism usually occur in veins of the lower extremities or of the pelvis It seems more than a coincidence that the apparent average time after operation at which thrombosis in these locations occurs corresponds to the period at which F-C time is great when contrasted with the preoperative circulation time That phlebitis and venous thrombosis occur seldom in the veins of the arms seems less strange with the knowledge that the A-C time is usually little changed postoperatively The implication is that slowing of venous circulation contributes to thrombophlebitis and venous thrombosis in the lower extremities We cannot emphasize that failure of venous circula-

tion to slow prevents these complications from occurring commonly in the upper extremities, for it does slow sometimes (table 1), although not as much or as frequently as it does in the legs

In the analysis of postoperative embolism, the figures of Barker and his co-workers<sup>5</sup> show that, while pulmonary emboli occur from the first to later than the twenty-fifth postoperative day, the highest incidence is from the sixth to the twelfth postoperative day. In the study of Barker and his co-workers<sup>6</sup> the highest incidence for postoperative embolism was noted on the eleventh postoperative day. It seems that the crux of the situation lies in the question as to when the thrombosis or extension of clot formation which leads to embolism has occurred. It seems true that if a thrombus remains in the femoral vein for as long as twenty-four hours there may be signs of beginning organization, which might be observed microscopically.<sup>7</sup> It has also been observed that in necropsies of patients with fatal pulmonary emboli it is often difficult to find the site of thrombosis. This would not be true if there had been organization of the clot. Moreover, examination of the embolus for signs of organization is almost invariably fruitless.<sup>7</sup> These facts would seem to indicate that the thrombus or the propagated portion of thrombus which broke loose to become an embolus was actually formed only a short time before pulmonary embolism occurred, probably within twenty-four hours before the embolism occurred. Hence it was formed at a time when the circulation time from the foot to the carotid sinus is usually increased.

We consider that there are three possible causes for phlebitis and venous thrombosis following operation: (1) increased tendency of blood to clot,<sup>8</sup> (2) injury to the intima of veins which serves as a locus for phlebitis or venous thrombosis,<sup>9</sup> and (3) slowed circulation in veins.<sup>10</sup>

5 Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T. Unpublished data.

6 Fifty per cent of instances of postoperative pulmonary embolism occurred from the seventh to the fifteenth postoperative day.

7 Robertson, H. Personal communication to the authors.

8 Allen, E. V. Changes in the Blood Following Operation, *Arch. Surg.* **15**: 254-264 (Aug.) 1927. Dawbarn, R. Y., Earlam, F., and Evans, W. H. The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, *J. Path. & Bact.* **31**: 833-873 (Oct.) 1928. Belt, T. H. Thrombosis and Pulmonary Embolism, *Am. J. Path.* **10**: 129-144 (Jan.) 1934.

9 Edwards, E. A. Observations on Phlebitis, *Am. Heart J.* **14**: 428-441 (Oct.) 1937. Cohnheim, J. Lectures on General Pathology, London, New Sydenham Society, 1889, vol. 1, p. 172.

10 (a) Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber, 1924, chap. 11, pp. 253-278. (b) Brown, G. E. Postoperative Phlebitis. A Clinical Study, *Arch. Surg.* **15**: 245-253 (Aug.) 1927. (c) Walters, W. A Method of Reducing the Incidence of Fatal Postoperative Pulmonary Embolism. Results of Its Use in Four Thousand and Five Hundred Surgical Cases, *Surg., Gynec. & Obs.* **50**: 154-159 (Jan.) 1930.



If increased tendency of the blood to clot were the sole cause of phlebitis and venous thrombosis, these should occur at any place in the body. Actually they occur selectively, chiefly in the lower extremities. However, intimal changes may have been present before operation in the veins of the legs, so that the tendency to thrombosis may be greater at this site. If the sole cause were damage to the intima of veins occurring at the time of operation, phlebitis and venous thrombosis should not occur after such operations as gastroenterostomy, for example, during which injury to the veins of the legs and of the pelvis presumably does not occur. Actually, venous thrombosis and pulmonary embolism occur after such operations. It may be significant, however, that the incidence of postoperative embolism is more than twice as great after hysterectomy as after cholecystectomy, which may indicate that damage to veins may be important in causing thrombosis leading to embolism in many cases (Barker and his co-workers<sup>5</sup>). If slowed venous circulation in the legs were the sole cause of phlebitis and venous thrombosis, perhaps they ought to occur much more frequently than they do, since the circulation in the veins of the legs slows at some time after operation in about 82 per cent of instances, whereas the incidence of postoperative venous thrombosis and pulmonary embolism following laparotomy is only about 2 per cent.<sup>5</sup>

We do not wish to imply that slowed venous circulation is the sole cause for phlebitis and venous thrombosis, for apparently it is not, but we do think that it is an important factor, and it may be of primary importance. All the factors mentioned previously may be important, and we are less interested in determining their comparative importance than in emphasizing that slowed venous circulation in the legs and, less remarkably, in the arms does occur after operation and that it seems to contribute importantly to the genesis of postoperative phlebitis and venous thrombosis. If it is justifiable to assume that slowed venous circulation is important in the genesis of postoperative venous thrombosis, it is important in consideration of pulmonary embolism following operation, since embolism originates from a clot in a vein involved by inflammation or by simple thrombosis. Naturally, individual cases of phlebitis, venous thrombosis or pulmonary embolism occurring at a time (within the first two days after operation, for example) when there seems to be no significant increase in F-C time cannot be accounted for by changes in the rate of venous circulation. Under such circumstances other factors are obviously more important.

It has been amply proved<sup>11</sup> that blood flow through an extremity varies widely. Recognition of the great influence of such factors as

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11 Freeman, N. E. The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* **113** 384-398 (Oct.) 1935. Youmans, J. B., Akeroyd, J. H., Jr., and Frank, H. Changes in the

temperature, exercise and position on the circulation time makes it apparent that there can really be no constancy of circulation time. As a matter of fact, it is impossible to obtain a true average circulation time unless it is an average for a stated set of conditions. It is not surprising, therefore, that venous circulation changes after operation. The difference in the influence of operation on A-C and on F-C time may depend on many things. Probably the two most important factors are (1) the difference in activity and in elevation of the arms and legs and (2) the temperature of the skin.

Many more movements are made with the arms than are made with the legs postoperatively. Repeated elevation of the hands above the level of the heart occurs. The legs are almost always below the level of the heart, and this situation is accentuated when the patient sits in bed, as he does during a good deal of his convalescence. We have shown<sup>1</sup> that elevation of extremities increases the rate of circulation in the veins of the arms. Exercises which we had our patients perform specifically for the purpose of studying the effect of exercise on the rate of venous circulation effectively decreased the F-C time but did not modify the A-C time significantly. This phase of the problem needs further consideration.

Moreover, the temperature of the skin of the toes is almost always less than that of the fingers. We have shown<sup>1</sup> that blood flows slowly in the veins of the extremities when the skin is cold and rapidly when the skin is warm.

If an attempt were made to depict the course of postoperative events in many cases (but not in all), the picture would probably be somewhat as follows. The patient who has had an operation for which a general anesthetic has been used returns to his room in good condition, with warm, flushed extremities and hence with faster blood flow in the peripheral veins (table 1). The cardiac output<sup>12</sup> is increased, and this

Blood and Circulation with Changes in Posture. The Effect of Exercise and Vasodilatation, *J Clin Investigation* **4** 739-753 (Nov) 1935. Ellis, L. B. Circulatory Adjustments to Moderate Exercise in Normal Individuals, with Particular Reference to the Interrelation Between the Velocity and Volume of the Blood Flow, *Am J Physiol* **101** 494-502 (Aug) 1932. Kvale, W. F., Smith, L. A., and Allen, E. V. Speed of Blood Flow in the Arteries and in the Veins of Man, *Arch Surg* **40** 344-351 (Feb) 1940. Smith and others.<sup>1</sup>

<sup>12</sup> Blalock, A. Cardiac Output in the Dog During Ether Anesthesia. I. The Effect of Ether Anesthesia on the Cardiac Output, *Arch Surg* **14** 732-751 (March) 1927. Snyder, J. C. The Cardiac Output and Oxygen Consumption of Nine Surgical Patients Before and After Operation, *J Clin Investigation* **7** 571-579 (Sept) 1938. Polano, H. Experimentelle Untersuchungen über das Verhalten des Minutenvolumens des menschlichen Herzens bei Athernarkose, Lumbalanästhesie und nach operativen Eingriffen (Bestimmung des Minutenvolumens nach Broxmeyer), *Deutsche Ztschr f Chir* **239** 505-513, 1933.

presumably increases the rate of flow of blood in the peripheral veins. This decrease of circulation time is contributed to by the common use of hot water bottles, elevation of the foot of the bed and restlessness of the patient.

On the second postoperative day the circulation time is about the same as it was before operation, and, provided there is not considerable fever, the F-C time begins to increase gradually. This may be because the patient soon sits up in bed, likes his room cooler, may begin smoking cigarets and becomes annoyed at slight discomforts and because removal of hot water bottles may allow his feet to remain cool or cold. Muscle tone may decrease.<sup>13</sup> Presumably all these things increase the circulation time, because venous blood seems to flow more slowly "uphill" and because cool environmental temperature, annoyance and cigaret smoking cause coolness of the skin, which appears to slow the flow of blood in veins. Disappearance of fever and return of cardiac output and pulse to normal allow slowing of venous circulation. Perhaps cessation of sedation and of intravenous injection of fluids may influence the circulation time. During this time, when more attention to his venous circulation is needed, the patient ordinarily receives none. A few days before he plans to leave the hospital, at a time when the circulation in the veins is markedly slowed, thrombophlebitis may occur, or a bland clot may form in a vein. When the patient becomes active, perhaps only to the extent of dangling the feet, or before this time, the clot becomes an embolus, or parts of it may separate from the vein and cause pulmonary embolism. Again, we wish to emphasize that we do not believe that increased circulation time is solely responsible for venous thrombosis.

If a maximal effort is to be made to prevent thrombophlebitis and venous thrombosis after operation, attempts should be made to reduce coagulation of the blood, to prevent injury to veins and to prevent slowing of the flow of blood in the veins of the legs. The first can be accomplished by injecting heparin intravenously, but heparin is expensive, the technic of administration is comparatively complex and discomfort occasioned by continuous intravenous administration is not negligible. This should be a reliable method of preventing postoperative venous thrombosis, although evidence is not conclusive on this point yet, as far as we know. Apparently nothing more can be done about the question of injury to veins than has already been accomplished by careful surgical technic. If roughening of the intima of veins in the legs exists before operation, nothing can be done to restore the intima to normal. It may be comparatively easy to increase the speed of flow

<sup>13</sup> Incomplete studies indicate that intramuscular tension decreases postoperatively in some cases. This may cause increased circulation time.<sup>1</sup>

of blood in veins of the extremities after operation, and this phase of the problem deserves further study. Theoretically, keeping the feet warm, exercise of the legs or a recumbent position with the foot of the bed elevated should prevent slowing of venous circulation after operation. We believe that the importance of increased circulation time in the genesis of postoperative venous thrombosis and pulmonary embolism can actually be determined in only one way, by preventing the decrease in speed of circulation in veins in a sufficiently large number of cases to determine the influence of this procedure on the incidence of venous thrombosis.

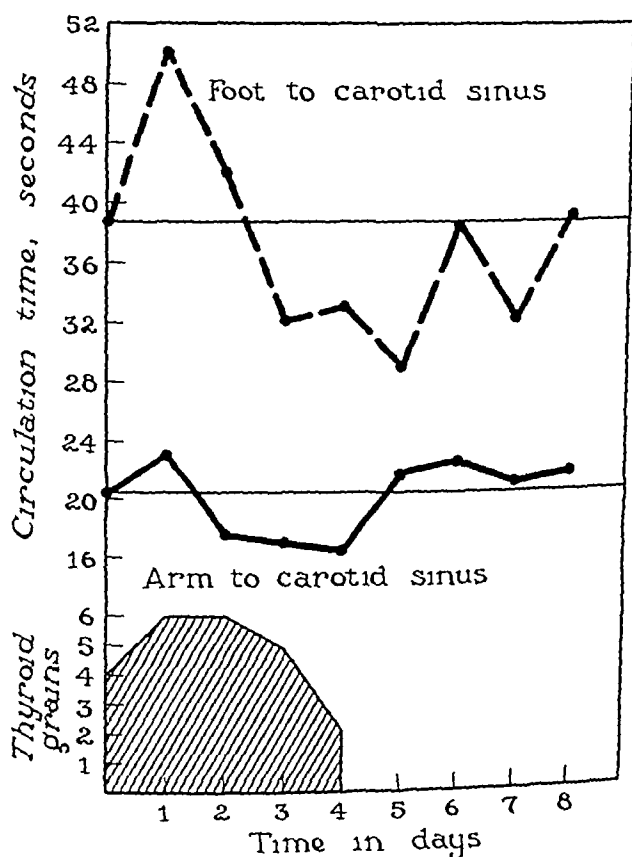


Chart 4—Effect of administration of thyroid on the circulation time in subjects on whom operation had not been performed

#### EFFECT OF ADMINISTRATION OF THYROID GLAND

*Normal Subjects*—Administration of thyroid gland decreases the circulation time, although at the end of a twenty-four hour period after beginning administration of it there is evidence of an increase. In our studies of 4 patients, decrease of the average A-C time was noted forty-eight hours after beginning a program of daily administration of thyroid, and decrease of the average F-C time was noted seventy-two hours after beginning such a program (table 3, chart 4). When administration

of thyroid was stopped, the A-C time of the only 2 patients on whom study was continued was normal in twenty-four hours. The average F-C time continued to decrease for twenty-four hours after cessation of administration and did not reach the value noted before administration until two to five days after cessation (table 3). The decreased venous circulation time which results from administration of thyroid seems to be brought about by tachycardia and vasodilatation.

*Subjects After Operation*—Thyroid extract was administered in doses of 2 to 6 grains (0.13 to 0.4 Gm.) daily, beginning two to five days postoperatively,<sup>14</sup> and reaching a maximum average dose between the second and the eighth postoperative day. The blocked curve representing the amount of thyroid administered to patients receiving it was obtained by averaging the amounts of thyroid for each postoperative day (chart 5). The average preoperative A-C time of twenty-five and eight-tenths seconds and the average preoperative F-C time of forty-two and five-tenths seconds were greater than the average normal values for these circulation times, probably because the patients were sick. The average circulation time for this group of patients did not increase after operation as it did in a group of patients who did not receive thyroid (charts 1, 2 and 3). The tendency of the curves to rise to the average preoperative level in the latter part of the study may have been the result of failure of reduced amounts of thyroid to offset the usual tendency for the F-C time to increase. Of greatest interest is the fact that the average A-C time and the average F-C time were less than the average preoperative circulation times throughout the period of convalescence, with 1 exception.

Analysis of the results in individual cases shows that the A-C time was rarely significantly greater after operation than before operation. In case 34, the F-C time was greater on the third postoperative day than before operation, but thyroid medication had been begun only on the third postoperative day. In case 36, the F-C time was greater on the third, fifth and ninth postoperative days (thyroid medication was begun on the third postoperative day). In case 37, the F-C time was persistently greater after operation than it was before operation, in spite of administration of thyroid. With the exceptions just noted the F-C time was not significantly greater after postoperative administration of thyroid was begun. The analysis of individual results emphasizes the errors which may result from using average values, which in this instance erroneously indicate that the F-C time did not increase after operation. It is obviously inadvisable to conclude that administration of thyroid prevents the increase in F-C time ordinarily noted following operation. However, our incomplete study indicates that it tends to

<sup>14</sup> The day of operation is considered the first postoperative day.

produce such a result<sup>15</sup> It is quite apparent that circulation time would not be influenced by thyroid administered on the same day on which a study of the circulation time was carried out In considering the relation of postoperative administration of thyroid to circulation time and pul-

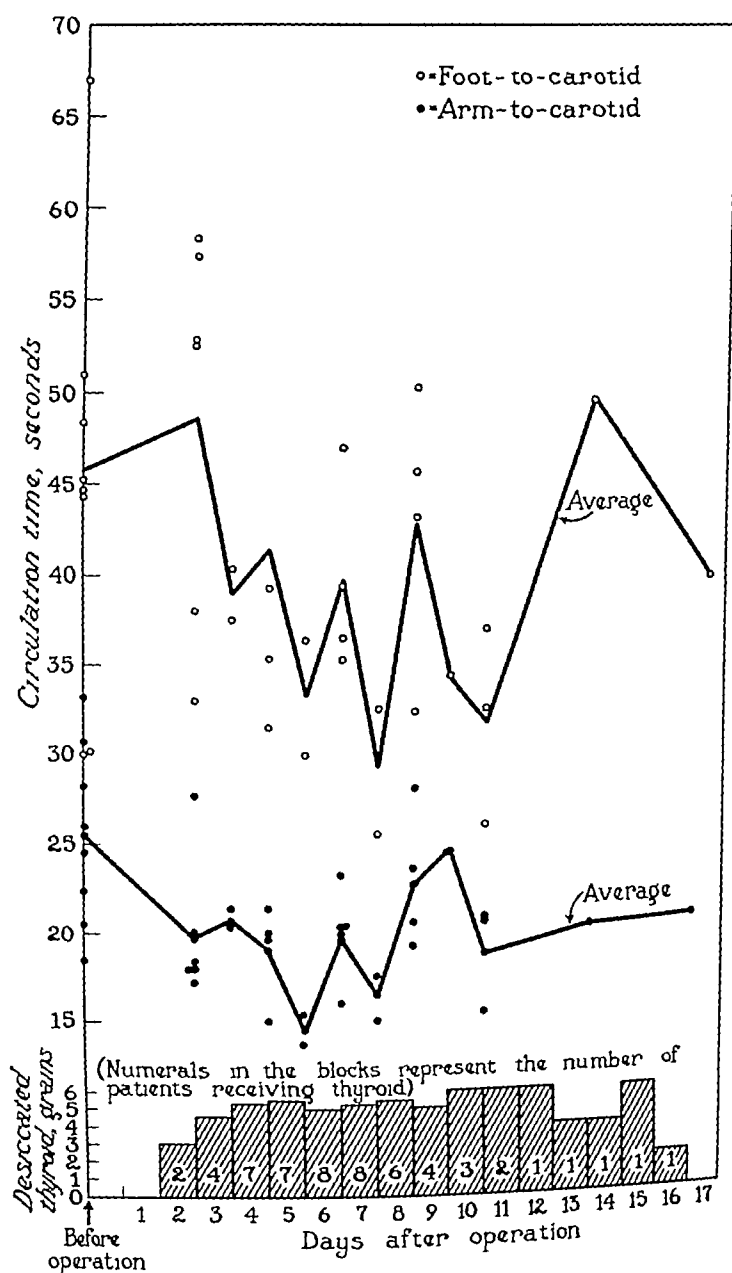


Chart 5—Effect of administration of thyroid on the circulation time in subjects on whom operation had been performed

monary embolism, it is important to consider the time of administration and the amount of thyroid and to bear in mind that in spite of judicious administration the venous circulation time may increase postoperatively.

<sup>15</sup> The report by Walters<sup>10c</sup> that postoperative administration of thyroid gland diminishes the incidence of pulmonary embolism is important

One should bear in mind that it is insufficient simply to administer thyroid after operation. One must know whether administration of it prevents slowing of venous circulation.

#### CONCLUSIONS

1 After operation the circulation time from the foot to the carotid sinus is usually increased after the fourth postoperative day, that is, blood flows more slowly. Increases in the circulation time from the arm to the carotid sinus are less common and less marked. The slowing of venous circulation probably is an important factor in the complicated mechanism of postoperative venous thrombosis and pulmonary embolism.

2 Administration of thyroid gland to normal subjects decreases circulation time, that is, increases the rate of flow of blood from the arm and from the foot to the carotid sinus. Postoperative administration tends to prevent the slowing of venous circulation which occurs commonly after operation.

# REVASCULARIZATION OF THE ISCHEMIC KIDNEY

GÉZA DE TAKATS, M D  
AND  
GEORGE W SCUPHAM, M D  
CHICAGO

The recent contributions of Goldblatt and his associates<sup>1</sup> have placed renal ischemia as a cause of hypertension in the center of interest. When the ischemic tissue was removed or when circulation was reestablished, the experimental hypertension disappeared. Goldblatt<sup>2</sup> made the significant observation that "if before constricting the renal artery the kidney is decapsulated and adipose or muscle tissue is attached to the denuded cortical surfaces, the accessory circulation from the adherent tissues becomes very prominent and interferes with the development of pronounced elevation of blood pressure." Animals survive complete closure of both main arteries "when effected gradually by increasing the constriction at intervals. This is proof that such accessory circulation can be functionally highly effective." Verney and Vogt<sup>3</sup> have observed that collateral circulation through the capsule or the hilus of the kidney may be sufficient to restore the increased blood pressure to normal in an animal with clamped renal vessels, they also found that extirpation of this collateral circulation raises blood pressure.

One of us (G de T) has been stimulated to experimental and clinical research on this problem by the investigations of Paunz,<sup>4</sup> undertaken at the University of Budapest, Hungary, between the years 1926 and 1930. This author first showed that an omental graft to the kidney

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From the Circulatory Group, St. Luke's Hospital, and the Department of Surgery, University of Illinois, College of Medicine.

1 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* **59** 347, 1934.

2 Goldblatt, H. Experimental Observations on the Surgical Treatment of Hypertension, *Surgery* **4** 483, 1938.

3 Verney, E. B., and Vogt, M. An Experimental Investigation into Hypertension of Renal Origin with Some Observations on Convulsive Uremia, *Quart. J. Exper. Physiol.* **28** 253, 1938.

4 Paunz, L. Die Inversion des Nierenkreislaufes, *Ztschr. f. d. ges. exper. Med.* **52** 548, 1926, Die Ersetzung der Vena renalis durch künstlich hervorgerufene Netzanastomosen, *ibid.* **59** 391, 1928, Die Erzeugung einer doppelten Blutkreislaufes in der Niere, *ibid.* **59** 280, 1928, Dauerversuch über die Ersetzung der Arteria renalis durch künstlich hervorgerufene Netzanastomosen, *ibid.* **71** 321, 1929.



could effectively drain venous circulation when the renal vein was obstructed, later he found that if he decapsulated and wrapped up one kidney in omentum, tied the renal artery of the same side one month later and subsequently removed the other kidney, the dog survived as long as one year, excreted 200 to 300 cc of urine daily, had normal concentrating and diluting power and showed only traces of albumin. When the animal was killed in perfect health, vascular granulations were found between the omentum and the scarified cortex of the kidney, but no dense scar tissue had formed. He kept a series of 18 dogs alive for varying periods. Recently MacNider and Donnelly,<sup>5</sup> using a similar technic of omentopexy, studied the growth of capillary buds in the normal kidney, they found them around the convoluted tubules but not in the vicinity of the glomeruli. The omental vessels showed hyperplasia of their walls as if increased blood flow had taken place through them. Davis and Tullis<sup>6</sup> placed omentum into the decapsulated and longitudinally split normal kidneys of dogs and later divided the renal vessels on the same side. The vascularization of the side operated on proved to be much greater than that of the control side, also the functional capacity of the operatively treated kidney seemed greater, as studied by the dye excretion and urea clearance tests. Mansfield, Weeks, Steiner and Victor<sup>7</sup> found that Goldblatt hypertension was reducible by implants of omentum or spleen into the kidney. The splenopexy gave longer lasting effects because of a greater development of collateral circulation. Goldberg, Rodbard and Katz,<sup>8</sup> however, could not obtain lowering of Goldblatt hypertension when they brought decapsulated kidneys into contact with denuded muscle, on the contrary, heavy scar tissue was found in the place of the renal capsule.

In unpublished and incomplete experiments undertaken between 1933 and 1936, Slaughter, Karstens, Bedinger and one of us (G de T) injected 10 per cent sodium morrhuate into the left renal artery and produced a small fibrous kidney within a month, this kidney was then decapsulated, scarified and wrapped in omentum, a month later, the right kidney was removed. Because of the variable response to the sclerosing solution and the presence of aberrant vessels, uniform atrophy

5 MacNider, W de B, and Donnelly, G L. Value of Omentopexy in Establishing an Adventitious Circulation in the Normal Kidney, *Proc Soc Exper Biol & Med* **40** 271, 1939.

6 Davis, H A, and Tullis, I F, Jr. The Effect of the Experimental Production of an Accessory Blood Supply upon Normal Kidney, *Proc Soc Exper Biol & Med* **40** 161, 1939.

7 Mansfield, J S, Weeks, D M, Steiner, A, and Victor, J. Reduction of Experimental Renal Hypertension by Pexis of Spleen or Omentum to Kidney, *Proc Soc Exper Biol & Med* **40** 708, 1939.

8 Goldberg, S, Rodbard, S, and Katz, L. Increased Collateral Blood Supply to the Kidney in Renal Hypertension, *Surgery* **7** 869, 1940.

could not be produced. Because of technical difficulties and especially because of Goldblatt's outstanding contribution to the production of uniform hypertension, these experiments were discontinued in 1936. Nevertheless, it was felt that these experiments more closely imitated arteriolar sclerosis in the kidney than did obstruction of the main artery, and the results were encouraging enough at the time to lead us to try renal revascularization on certain patients suffering from renal vascular damage.

Our first patient, Alma J., was operated on in April 1936, at which time muscle flaps were sutured around the decapsulated and scarified kidney on both sides. Since that time, 2 more patients (cases 3 and 4) have had a similar operation, but unilaterally, in case 2, omentum was used to cover the kidney.<sup>9</sup> Recently (January 1939) Abram, Iselin and Wallich<sup>10</sup> reported 1 case of chronic glomerulonephritis and another of malignant nephrosclerosis in which unilateral omental transplants were done, both cases were reported within three months of the operation, and no results were obtained.

#### REPORT OF CASES

CASE 1—In April 1936, Alma J., a pale, thin woman aged 39, was referred to the neurocirculatory clinic at St. Luke's Hospital by Dr. Thomas J. Fentress. She complained of severe headaches, ringing in the ears, blurred vision and extreme nervousness. She had not been seriously ill until the age of 35, when her blood pressure was first examined because of frequent headaches. The systolic blood pressure dropped from 285 to 158 mm. of mercury after three months of rest in bed. Again, in January 1933, her blood pressure reached 250 mm. of mercury. On examination at the Mayo Clinic, in April 1934, her blood pressure was 252 mm. of mercury systolic and 140 diastolic. A report obtained of her status then revealed a normal blood count, a negative reaction for syphilis and a value for blood urea of 38 mg. per hundred cubic centimeters. An electrocardiogram showed a rate of 72, sinus rhythm, a slurred QRS complex in derivation III, left ventricular preponderance, diphasic P waves in lead IV and inverted T waves in leads II and III.

Physical examination disclosed slight left ventricular hypertrophy, with forceful pulsation at the apex, and hyperactive reflexes of the left upper extremity, with fleeting paralysis. There was papilledema of 3 D. on the right and 2 D. on the left. The retinal vessels were constricted and tortuous. There were no hemorrhages or exudates (Dr. Frank Brawley). The concentration-dilution test showed the specific

<sup>9</sup> A fifth patient, a 7 year old girl, was operated on in February 1940, omentum being used on one side and a pedicled muscle flap on the other. This child had bilateral congenital hypoplasia of both kidneys, producing severe hypertension. The case will be reported in detail after a longer period of observation. Six months after the operation the child was free of headaches and dizziness and gained strength and weight. A bilateral transdiaphragmatic splanchnic section has been performed in addition.

<sup>10</sup> Abram, P., Iselin, M., and Wallich, R. Essai de traitement de l'hypertension arterielle, d'origine renale par la revascularisation chirurgicale du rein (nephro-omentopexie), *Presse med.* 47: 137, 1939.

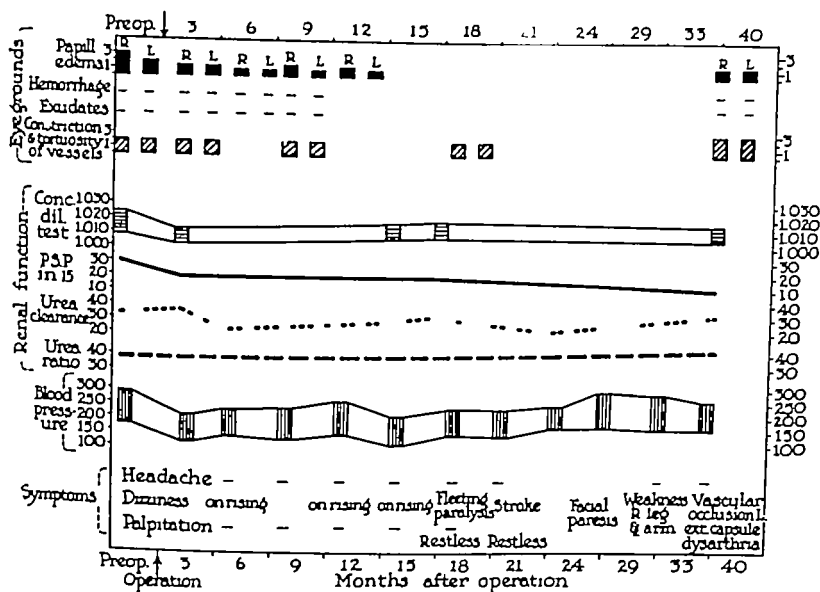


Fig 1—Preoperative and postoperative records of Alma J, 39 years old. During a postoperative course of forty months the eyegrounds showed no significant change except fluctuations in papilledema, which is not easy to measure accurately. In spite of repeated cerebral vascular accidents, no retinal hemorrhages or perivascular exudates were seen, constriction and tortuosity of the retinal vessels were measured on the basis of 1 plus to 4 plus. The specific gravity of the urine varied from 1 025 just prior to operation to its lowest figure, 1 013, three months after the operation. At the end of forty months, the specific gravity was 1 016. Dilution varied from 1 004 at three months, to 1 008 at twelve months, which was also a preoperative figure. The fifteen minute excretion of phenolsulfonphthalein was 30 per cent prior to operation and 20 per cent at three months and twelve months after operation, it declined to 10 per cent at last examination. The standard urea clearance of 33.8 cc of blood per minute fluctuated slightly during the postoperative course but was still 31.2 cc. per minute at the forty month observation. The urea ratio ( $\frac{\text{urea N} \times 100}{\text{NPN}}$ ) was 37 preoperatively, remained the same three months later, rose slightly to 39 at the end of the twenty-first month and was 43 at the end of forty months. The blood pressure varied from the maximum of 300 systolic and 170 diastolic at the twenty-fourth month, during an acute attack of hypertensive encephalopathy, to the minimum of 214 systolic and 140 diastolic fifteen months after operation. Of the subjective symptoms prior to operation, dizziness on rising always persisted, after a vascular accident occurring thirty months postoperatively, weakness in the right arm and leg became pronounced. The chart shows a slight but definite progress in renal damage indicated by the fifteen minute phenolsulfonphthalein test, the concentrating ability and the urea ratio, the heart remained remarkably unaffected during this period. The hypertensive encephalopathy progressed from a prodromal symptom of fleeting paralysis in one arm to massive vascular occlusion in the external capsule on the left, this will probably cause death.

gravity of the urine to be from 1 008 to 1 025. The rate of phenolsulfonphthalein excretion was 30 per cent in fifteen minutes and 65 per cent in two hours. The urea ratio was 37. A diagnosis of severe benign nephrosclerosis was made.

On April 9, 1936, through a lumbar incision and with resection of the tip of the twelfth rib, the left kidney was exposed. It was small and firm and showed depressed scars over the cortex. Decapsulation was easy. The cortex was scarified with a scalpel, a pedicled flap of the musculus quadratus lumborum, 8 cm. in length and 3 cm. in width, was swung around the kidney and anchored with a few interrupted sutures. Closure was made with an all-silk technic, in layers.

On April 20 an identical exposure was made and the same procedure was done on the right side. The right kidney seemed somewhat larger and softer than the left.

Uneventful convalescence followed this two stage operation. Subjectively, headaches, heart consciousness and dizziness disappeared and did not recur. Dizziness returned ten months after the operation, but only on rising suddenly. A year after operation there were still no headaches. At eighteen months fleeting paralysis of the arm was noted, and at twenty months a stroke occurred. At twenty-four and twenty-nine months residual paralysis was obvious. At forty months a major vascular occlusion occurred in the region of the external capsule of the brain on the left, leading to dysarthria and marked mental deterioration. During this entire postoperative period, however, there was no marked change in the retinal findings, in the renal function or in blood pressure, although at the end of forty months the fifteen minute phenolsulfonphthalein test showed diminishing renal function (fig 1).

*Summary of Case*—A 39 year old woman suffered from severe benign nephrosclerosis (no retinal exudates and hemorrhages). She was treated by bilateral implantation of pedicled muscle flaps into the scarified kidney. Her postoperative course indicates a progressive development of hypertensive encephalopathy, without significant deterioration or improvement of renal function.

CASE 2—F P, a 29 year old man, was referred by Dr Harold Lueth to the Research and Educational Hospital of the University of Illinois from the Evanston Hospital, which he had entered because of palpitation, precordial soreness, dizziness and poor vision. In 1925 the patient was first discovered to have hypertension. Although he had been bothered for the past eight years with poor vision and nycturia, he had felt well until six and one-half weeks before entrance to the hospital, at which time he had a severe spell of dizziness, headache and nausea. He stated that he had had a severe headache ever since. He could not read a newspaper with his left eye. At the age of 8 he had scarlet fever, which was not known to have been followed by nephritis. His father died of apoplexy, his mother had high blood pressure. Examination of the ocular fundi showed papilledema of 2 D on both sides, tortuous spastic vessels with perivascular infiltrations and recent and old hemorrhages. The heart was enlarged to the left, the aortic arch was dilated. The urine contained from 2 to 6 Gm of albumin daily. The concentration dilution test showed the specific gravity of the urine to range from 1 020 to 1 015, the urea clearance was 12 05 cc per minute, and the urea ratio was 51. The rate of phenol sulfonphthalein excretion was 19 per cent at forty-five minutes and 40 per cent at one hour and forty-five minutes. The blood pressure varied from 230 to 200 mm. of mercury systolic and from 156 to 136 mm. diastolic. Nine grains (0 58 Gm) of sodium amytal did not lower his blood pressure, which also failed to respond to potassium sulfocyanate. The electrocardiogram showed marked myocardial infarction. On Feb 2, 1939 a typical nephro-omentopexy was done by bringing up a flap of omentum through the peritoneum and wrapping it around the decapsulated

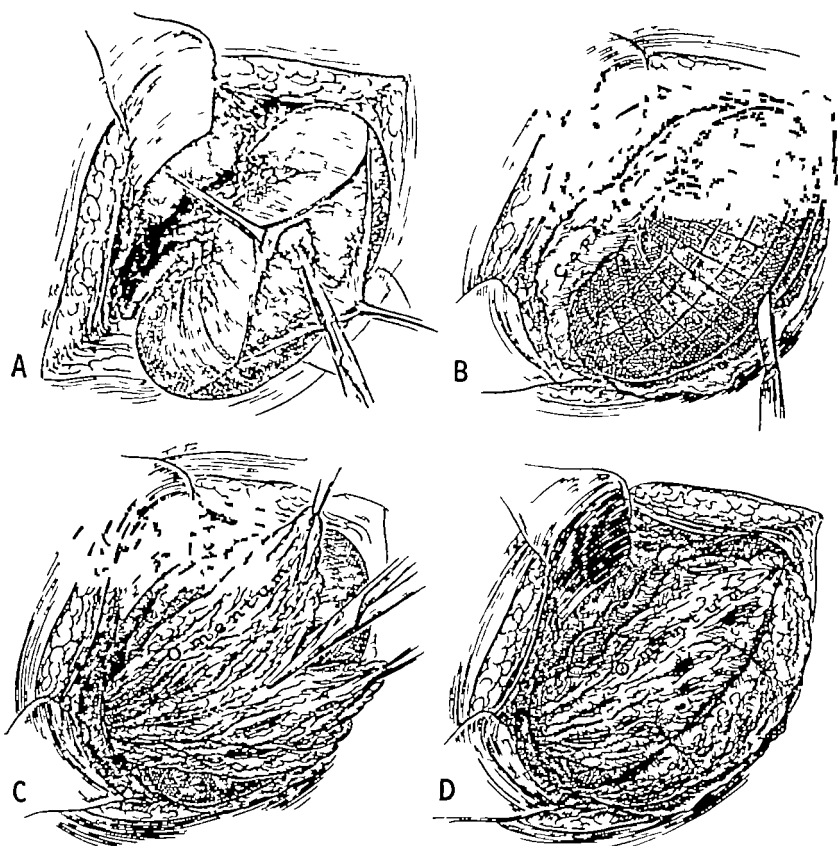


Fig 2—A, the kidney is exposed in the usual manner, in some cases a high muscle-splitting incision of the anterior abdominal muscles is done as for lumbar sympathectomy, so that a large lateral peritoneal surface is available. The kidney is delivered into the wound, and a longitudinal incision is made on its convexity. The capsule is grasped with Allis forceps and stripped of the cortex with a small moist pledget of cotton. B, after the capsule is reflected as far as the pedicle of the kidney, the cortex is scarified with the edge of the scalpel to prepare the kidney for the graft. A deeper incision is made on its convexity. The oozing must be stopped with hot saline compresses. C, a small incision is made in the peritoneum medial and caudal to the pedicle of the kidney, a flap of omentum is delivered and carefully split in the middle. The omentum is anchored to the peritoneal slit with a few interrupted sutures. D, the scarified kidney is wrapped in omentum which covers both the anterior and the posterior surface. A few interrupted sutures anchor the omental flaps to the reflected capsule and to each other. Enough space should be left to allow for drainage of any blood accumulating between the omentum and the kidney. A large hematoma, when organized, may readily form a heavy scar around the kidney and completely defeat the purpose of the operation.

and scarified right kidney (fig 2) The kidney seemed small and firm, with whitish scars on the surface A biopsy specimen taken from its cortex showed arteriolar sclerosis, with mostly intact glomeruli (fig 3)<sup>11</sup>

The postoperative course was uneventful Five months after the operation the patient was readmitted for a postoperative study He complained of marked dizziness and a discharge from the right ear, which had been intermittently present ever since he had had scarlet fever at the age of 8 The blood pressure was 276 systolic and 184 diastolic Potassium sulfocyanate, 3 grains (0.19 Gm) three times a day, was given but could not be tolerated Ten per cent dextrose had to be given intravenously for several days, in five days he could again take food by mouth His dizziness improved, but only if he stayed in the horizontal position His heart



Fig 3 (case 2) —Renal biopsy specimen from F P Generally speaking, the glomeruli are fairly well preserved About 15 per cent of them, however, show varying changes, beginning with obliteration of the capillary loop boundaries, swelling of the epithelium with proliferation of the cells and swelling of the endothelium Occasionally synechiae are demonstrable between a portion of the glomerulus with the Bowman's capsule A few of the glomeruli are shrunken and even obliterated, with secondary hyalinization Some of Bowman's capsules are markedly thickened by dense fibrous tissue Such glomeruli are accompanied by thickening of the afferent and efferent arterioles as a result of fibrous tissue proliferation and hyalinization Not infrequently the lumens are not discernible, or hyalin may replace the entire structure The walls of the interlobular arteries are thickened and show similar changes

The convoluted tubules seem to be reduced in number, the nuclei of the lining epithelium are pyknotic The interstitial tissues show moderate fibrosis The capsule of the kidney is thickened and shows regular depressions Adjoining the latter areas the collecting tubules are dilated There is no evidence of arterial necrosis anywhere. Note the marked arteriosclerosis in the center of the field

<sup>11</sup> The study of renal biopsy specimens was made by Dr Sol R. Rosenfeld

became enlarged to the left. Bilateral choked disks were present. The acute edema of the brain was finally relieved. On July 23 he could be up and about without dizziness or headaches. His blood pressure fell to 230 systolic and 160 diastolic. The urea clearance was 33.2 cc per minute, and the urea ratio was 57, showing an improvement in urea clearance but a deterioration of the urea ratio. The daily excretion of protein dropped from 14 Gm at the second admission to 5 Gm at discharge.

A third admission was made to the Evanston Hospital seven months after the operation. The patient had had several attacks of cerebral edema meanwhile and had suffered from severe headaches, nausea and vomiting. Between these attacks he was fairly comfortable. On entrance the heart was enlarged to the midaxillary line, there was moderate edema of the legs and ankles, and the face was puffy. The blood pressure ranged from 250 to 220 systolic and from 170 to 160 diastolic. The edge of the liver was palpated at the level of the umbilicus. Ophthalmoscopic examination showed three fresh hemorrhagic areas in the left fundus. The specific gravity of the urine was fixed at 1.010. A phenolsulfonphthalein excretion of 7 per cent could be obtained at ninety-five minutes. The urea clearance showed 29 cc of blood cleared of urea per minute, 55 per cent of the average normal function. The electrocardiogram showed no change as compared with former tracings.

The patient was dehydrated with ammonium chloride and mercupurin (a mercurin-theophylline preparation) several times, which resulted in marked diuresis. The level of nonprotein nitrogen, however, varied from 70 to 100 mg per hundred cubic centimeters, the value for urea nitrogen, from 48 to 56 mg per hundred cubic centimeters and the urea ratio, from 69 to 75.<sup>12</sup>

*Summary of Case*—A 29 year old man was subjected to unilateral nephro-omentopexy. At the time of operation he had obvious signs of fulminating malignant nephrosclerosis. Section of the splanchnic nerve in such a patient has never been of any benefit. The omental graft similarly failed to make an impression on the course of the disease. Death from uremia occurred ten months after the nephro omentopexy.

*CASE 3*—Shirley S., a 7 year old girl,<sup>13</sup> was referred to the Research and Educational Hospital by Dr Woodruff L. Crawford of Rockford, Ill. She was admitted on March 1, 1937, with a history of vomiting spells, headaches and convulsions. Choked disks and high blood pressure were discovered by Dr Crawford, who sent the patient for observation and possible treatment. Symptoms had been present for about two years.

The girl was pale and undernourished. She showed marked cutis marmorata. Both papillae showed edema of between 5 and 6 D. The heart was enlarged to the left, the aortic and pulmonic second sounds were accentuated, without murmurs. There were no palpable masses in the abdomen. The reflexes were normal. Dr Eric Oldberg found nothing to suggest a brain tumor. The blood count and the

12 On November 26, approximately ten months after the operation, the patient died at the Evanston Hospital. At autopsy the flap of omentum was seen firmly attached to the lower pole of the right kidney. Vessels were well visible coursing through the flap. The fat had completely disappeared. Sections taken from this kidney and the left one showed no changes compared with the section obtained through the biopsy specimen. The heart was markedly enlarged to the left, death resulted from terminal uremia.

13 This patient was in the pediatric service of Drs Hess and Poncher, who gave permission for perusal of the history.

urine were normal. The blood pressure fluctuated from 290 to 230 mm of mercury systolic and 190 to 160 mm diastolic. A daily blood pressure curve was charted for several months but was lost between departments. The fluctuations of blood pressure were so marked that pheochromocytoma of the adrenal or of the paraganglions was suspected. A retrograde pyelogram revealed that the right kidney was larger than the left, and questionable clubbing of some of the calices on the left side was reported. A concentration-dilution test of the urine showed a specific gravity between 1.024 and 1.008. The phenolsulfonphthalein excretion was 50 per cent in one-half hour, 65 per cent in one hour and 80 per cent in two hours. The urea clearance was 31 per cent and 32 per cent. The values for nonprotein nitrogen were 36, 29, 27 and 39 mg per hundred cubic centimeters. The value for urea nitrogen was 15 mg per hundred cubic centimeters, the urea ratio was 51. Excretion of lead in the urine was within normal limits for this area.

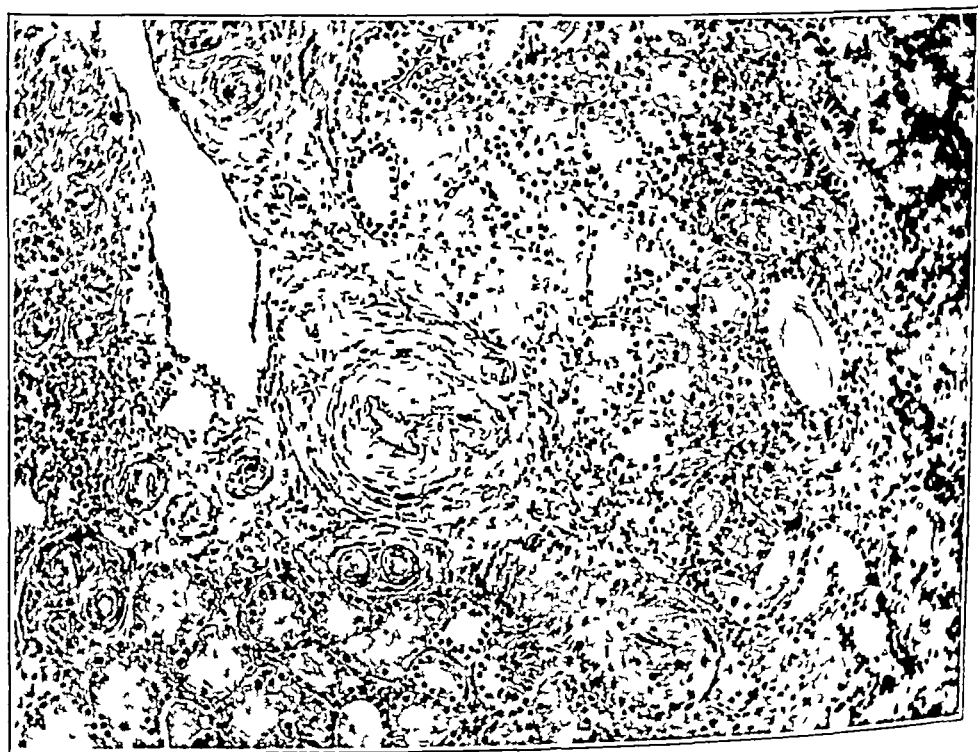


Fig. 4 (case 3) — Specimen from the right side (hypertrophic). The majority of the glomeruli seem well preserved, some of them show shrinking and fibrosis. The small and medium-sized arteries, where visible, show marked thickening of their walls, with almost complete obliteration. The intralobular arteries and the arcuate arteries show slight to no change. The tubules in the cortex show alternating areas of distention and collapse. In the latter areas the interstitial tissue is markedly increased. The capsule is depressed at regular intervals. At the site of depression the fibrous areas just described are observed. The pelvis presents a loss of epithelium with edema and fibrosis of the subepithelial tissues. Note the marked hyaline arteriosclerosis in the arterioles and small arteries.

The girl had severe hypertension, papilledema and increased size of the heart and aorta. The total renal function was remarkably good, although the urea clearance rate and the urea ratio showed indications of impairment. The operation was undertaken to explore the left adrenal region, as the hyp



showed paroxysmal fluctuation varying as much as 100 mm of systolic pressure. She had one severe attack of hypertensive encephalopathy, during which she almost died of acute cerebral edema.

On April 13, 1937 the left kidney and adrenal gland were explored. The left kidney was small and very firm and showed a granular surface, it revealed multiple areas of pitting and had the appearance of nephrosclerosis. A small wedge of renal tissue was taken for biopsy. The left adrenal gland seemed slightly enlarged, although the surgeon (G de T) was unable to be sure how large a 7 year old child's adrenal should be. It seemed firm and had the consistency of a rabbit's ear. In the retroperitoneal space there was a long chain of grayish hyperplastic lymph glands. A biopsy specimen was taken of these for identification. Closure of the wound was made with silk.



Fig 5 (case 3)—Specimen from the left side (atrophic). The section of the kidney is divided into two distinct parts connected by dense fibrous tissue, proliferating tubules and thickened arteries. To one side of this junction the renal architecture is obscured, and there one notes hyalinized, thickened and obliterated vessels and perhaps glomeruli interspersed with small tubules with deeply staining nuclei and hyaline casts in the lumens. Round cells are numerous within the dense fibrous interstitial tissue. To the other side glomeruli are found, which are normal in appearance but in more instances are surrounded by fibrous tissue and atrophic tubules. The arterioles and small arteries in the main show no thickening. The intralobular arteries show slight to no thickening except for an occasional thickened vessel.

The tubules show areas of slight dilatation alternating with areas of compression, fibrosis and even proliferation. The capsule is slightly thickened and depressed, corresponding to interstitial fibrosis.

The diagnosis was right kidney, moderate arteriolosclerosis, left kidney, complete atrophy of one portion and slight arteriolosclerosis of the remaining portion.

The child stood the operation well. The renal biopsy revealed marked arteriolar obliteration, with preserved glomeruli and no stasis in the vascular tree. In the removed lymph glands the arteriolar changes were even more extensive.

On April 27, two weeks later, the right side was similarly explored. The right kidney was much larger and softer than the left. The right adrenal was smaller and more friable than the left. Because the presence of an adrenal tumor had been excluded, the right major, minor and minimal splanchnic nerves were identified under the diaphragm and were traced and sectioned at their entrance into the celiac ganglion. The right kidney was then decapsulated and scarified, and a piece of muscle with a broad pedicle was swung around the raw surface of the kidney. There was very little oozing. During this procedure the blood pressure fell to 90 mm of mercury systolic and 80 mm diastolic but was restored by two doses of neosynephrin hydrochloride. Closure was made in layers, with silk and without drainage.

The child's convalescence was uneventful, the wound healing by primary intention. The blood pressure, however, did not change, although it seemed more stable. The girl had several spells of cardiac asthma and became edematous. The liver became enlarged, the heart, especially the right side, was enlarged. She was given digitalis and was in an oxygen tent for three weeks before death, which occurred on June 7, six weeks after the second surgical procedure.

Autopsy revealed left ventricular hypertrophy, with moderate dilatation of all chambers of the heart, atelectasis of the lower lobe of the right lung, fatty changes in the liver, marked bilateral nephrosclerosis with atrophy of the left kidney, and edema of the brain with slight hydrocephalus.

The left kidney weighed only 37 Gm, the capsule was thick and stripped with difficulty, leaving a rough, reddish brown granular surface, the right kidney weighed 62 Gm, and a thick, well adherent mass surrounded the decapsulated kidney. Histologic sections of the two kidneys (figs 4 and 5) showed no marked difference between the two sides. The glomerular tufts were filled with red cells. The convoluted tubules were in a severe stage of degeneration. The collecting tubules contained many hyaline casts. Some of the glomeruli were very cellular, and the capillary epithelium appeared slightly thicker than normal. The smaller vessels showed marked intimal proliferation, almost to occlusion of the lumen, and the medium-sized vessels showed intimal thickening and some thickening of the muscularis. The histologic diagnosis was nephrosclerosis, with complete atrophy of one part of the left kidney.

*Summary of Case*—A 7 year old girl, suffering from a severe fluctuating type of hypertension, choked disks, convulsions and vomiting spells showed no adrenal tumor on exploration, but there was marked hypoplasia of one kidney, with compensatory hypertrophy of the other. Superimposed on the congenital anomaly was malignant nephrosclerosis. Cardiac compensation was maintained with difficulty. A unilateral decapsulation and application of a muscle flap did not arrest the disease, which ended in cardiac failure.

**CASE 4**—Mrs Rose B, 32 years old, had suffered from lupus erythematosus for eight years. She had received several treatments with sodium thiosulfate. Her blood pressure was 125 systolic and 74 diastolic in December 1935 and 138 systolic and 90 diastolic in June 1938. Her mother had diabetes and hypertension. In May 1934 the patient had eclampsia and miscarried in the sixth month of pregnancy. In 1935 she again had eclampsia when five and one-half months pregnant. The blood pressure then was 214 systolic and 140 diastolic. A cholecystectomy was performed in June 1934 and a salpingo-oophorectomy in 1935; neither of these operations affected the lupus. In July 1938 she suddenly, ex-

numbness in both feet, this symptom gradually disappeared in two to three months, but cramping of the calves remained, at the time of admission she could hardly walk half a block. There were also some tingling and itching of the hands, occasionally red splotches would appear, which would disappear in two or three days.



Fig 6—*A*, intravenous pyelogram of Mrs R B taken ten minutes after injection of diodrast. The right renal pelvis (at left of photograph) is well filled with the dye and shows normal contours. There is no trace of dye on the left side. *B*, intravenous pyelogram taken forty-five minutes after injection of diodrast. The right renal pelvis (at left of photograph) is almost empty. The left pelvis has just filled, it was invisible at thirty minutes.

On her entrance to St Luke's Hospital, March 6, 1939, butterfly areas of lupus erythematosus were found on the cheeks and faded spots on the arms and upper part of the chest. The pulses were impalpable on the lower extremities,

including both femoral pulses at the groin. The radial arteries pulsated well. The blood pressure was 170 systolic and 120 diastolic. It did not fall on administration of nitrites or of pentobarbital sodium. The oscillometric index at the left ankle was 0.5 cm at 80 mm of mercury and was the same at the right ankle. The upper part of the left arm showed an oscillometric index of 3 cm at 120 mm of mercury on the left and 3 cm at 140 mm on the right. The urine was normal, the urea clearance was 29 cc of blood per minute, and the urea ratio was 38. The eyegrounds were normal. An intravenous pyelogram showed the dye in five minutes in the right kidney but not before the end of forty-five minutes on the left side (fig 6). Cystoscopic study and ureteral catheterization (Dr W J Baker) revealed that the urine from the right ureteral orifice was deep amber and that from the left pale and watery. The intravenous phenolsulfonphthalein appeared on the right side in four and one-half minutes, with excellent concentration, but none had appeared from the left side in fifteen minutes. Dr E H Oliver thought that the lupus was quiescent and that previous surgical operations had caused no flare-up of the condition.

The history of eclampsia, the prolonged treatment with a gold compound and the presence of lupus erythematosus suggested a vascular lesion in the kidney, in addition, the occlusion in both iliac arteries and possibly the aorta suggested a Goldblatt kidney. The diagnosis of endocarditis as described by Libman in connection with lupus erythematosus could not be made. The possibility of periarteritis nodosa was suggested by Dr R W Keeton<sup>14</sup>.

Operation (on March 11) was undertaken with the idea of exploring or possibly revascularizing the left kidney and at the same time sectioning the lumbar sympathetic nerves to improve circulation to the left lower extremity. The aorta, exposed by an anterolateral muscle-splitting incision, was small and collapsed and did not pulsate at the level of the umbilicus. The lumbar portion of the sympathetic chain was removed on the left between the first and the third lumbar ganglion. The left kidney was exposed. It was of normal color but definitely small, with small cortical scars and fatty deposits. A section removed from its middle third hardly bled (fig 7). The pedicle pulsated, but more feebly than on the other side. Distal to the aorticorenal junction the aorta was pulseless, proximal to it there was strong pulsation. The kidney seemed like a Goldblatt kidney, but because of the lupus and its possible effect on the other kidney the thought of a nephrectomy was abandoned. The left kidney was decapsulated, scarified and wrapped in a pedicled flap taken from the psoas muscle. Closure was made with an all-silk technic, with out drainage.

The patient stood the operation well, her blood pressure remained elevated and stable throughout the operation. However, on the third day a rise in temperature occurred, together with gallop rhythm, some pulmonary congestion and edema of the ankles. Dr R W Keeton ordered administration of digitalis and restriction of fluids, under this management the gallop rhythm subsided, and the process in the left lung did not progress. On the fifth postoperative day the patient seemed definitely better and was taking foods and fluids by mouth. However, at the end of the fifth day there occurred a sudden severe pain high over the dorsal part of the spine and the chest, and the gallop rhythm returned. The temperature rose to 102. A portable x-ray apparatus showed a questionable shadow behind the heart in the posterior mediastinum (Dr E L Jenkinson), but an oblique view could not be obtained with the portable apparatus. The patient became toxic and delirious.

14 In a recent case of lupus erythematosus, Dr Gracy B Mallory made a pathologic diagnosis of periarteritis nodosa (Cabot Case 24201), *New England J Med.* 218:838 [May 19] 1938.

expectorated dark, frothy mucus in large quantities gradually cyanosis set in, which did not improve with digitalis and oxygen therapy. On the sixth day difficulty in swallowing occurred. The toxicity increased, and the patient died, seemingly from pulmonary edema, on the sixth postoperative day. Permission for autopsy could not be obtained. As a cause of death, reactivation of the lupus erythematosus was suggested by the high temperatures, the marked toxicity, an unexplainable septicemia with sterile blood cultures and the absence of reaction in the wound. But the questionable shadow in the mediastinum, the pain in the chest, the difficulty in swallowing and the cardiac insufficiency made one wonder whether ascending aortic thrombosis was not present.

*Summary of Case*—A 32 year old woman suffering from lupus erythematosus, unilateral renal disease, hypertension and vascular occlusion of the aorta was sub-



Fig 7—Photomicrograph (Mrs R. B.) The glomeruli show no abnormal changes except for thickening of Bowman's capsule. The arterioles and arteries show slight to no thickening. The most striking changes are in the interstitial tissues. There are focal areas of infiltration of large lymphocytes and plasma cells. There seems also to be an increase in the interstitial fibrous tissue. In some areas compression and obliteration of the convoluted tubule can be seen.

The impression was that of interstitial lymphoblastic plasmocellular nephritis with fibrosis. There was moderate arteriolar obliteration.

jected to an exploratory procedure and lumbar sympathectomy, and a left renal vascularization was performed. She died six days after the operation. The cause of death was not determined. Biopsy revealed nephritis, which is not infrequently associated with lupus erythematosus.

#### COMMENT

The 4 cases presented differ greatly, and it may be well to deal with them individually. The first case is perhaps the most instructive, because

follow-up records are now available since April 1936. The condition had to be classified as benign nephrosclerosis because of the absence of retinal hemorrhages and exudates, but definite impairment of renal function was present. The urea clearance and urea ratio have not changed appreciably for four years. Nor has the heart shown any deterioration, as checked by physical findings and electrocardiograms. The vascular encephalopathy, which manifested itself as the earliest symptom in fleeting paralysis of the arm, progressed to hyperactive reflexes, headaches, papilledema and blurred vision, and, after repeated strokes, mental deterioration is now in its terminal stage and will most likely be the cause of death. That such cerebral episodes are not dependent on renal function was first convincingly demonstrated by the work of Volhard<sup>15</sup>. Neither the tests of renal function nor the nitrogen retention showed any deterioration of renal function while the cerebrovascular episodes repeated themselves. The statistics of Christian<sup>16</sup> show that, of 131 patients who died of hypertension in the hospital, 32 per cent died of cardiac failure, 25 per cent of cerebral accidents, 25 per cent of conditions independent of hypertension and only 4.5 per cent of uremia or with severe renal disease. Similarly, Bell and Clawson<sup>17</sup> found that of 420 patients who died of essential hypertension, 49.3 per cent died of cardiac failure, 19 per cent of cerebral apoplexy or thrombosis, 15 per cent of coronary disease, 10 per cent of accidents or intercurrent disease and 8.6 per cent of renal disease. The cause of death from renal failure is thus the least frequent of all causes of death from essential hypertension, and it would seem that, once the arterial hypertension has persisted for a time, vascular damage in different organs and failure of the heart will be the causes of death. Less than 10 per cent of the patients survive long enough for renal failure to occur.

Therefore we do not feel that the process in the case of Alma J. has been influenced, even though renal impairment has not progressed since the operation.

Even more clear is the progress of nonrenal vascular damage in the case of F. P. (case 2). The malignant nephrosclerosis in this patient, a 29 year old man, obviously carried the worst possible prognosis. The medical department felt that in such a hopeless case any surgical procedure is justified. But the surgeon may just as well accept a patient with inoperable carcinoma in the terminal stage as try to save a patient

<sup>15</sup> Volhard, F., in Mohr, L., and Staehelin, R. *Handbuch der inneren Medizin* Berlin, Julius Springer, 1918, vol. 3, pp. 139-168.

<sup>16</sup> Christian, H. A., in discussion on Andrews, C. L. *Circulatory Tension Versus Circulatory Depressants in Cardiovascular Renal Disease with Hypertension*, J. A. M. A. **87** 928 (Sept. 18) 1926, in discussion on Paullin, J. F. *Ultimate Results of Essential Hypertension*, *ibid.* **87** 925 (Sept. 18) 1926.

<sup>17</sup> Bell, E. T., and Clawson, B. J. *Primary (Essential) Hypertension*, *ibid.* **5** 939 (June) 1923.

with a diffuse arteriolar lesion in many organs. This patient died ten months after the operation, with gradual failure of his cardiovascular and renal systems.

The third case, that of a 7 year old child, varies from the first 2 in causation of the condition. The type of juvenile malignant nephrosclerosis in conjunction with congenital hypoplasia of one kidney observed in this case has been discussed by Ask-Upmark,<sup>18</sup> who published 6 cases in which autopsy was performed. The anomalies consisted of unilateral hypoplasia, absence of cortical tissue with development of blind subcapsular diverticula communicating with the pelvis of the kidney and, finally, cystic spaces filled with colloid material. Normal kidney tissue alternated with normal renal parenchyma. We have observed 1 case besides the one described, this was the case of an 8 year old girl suffering from malignant nephrosclerosis, in whom perirenal insufflation revealed marked hypoplasia of one kidney, she was seen at a terminal stage of cardiac failure, and operation was not considered.

If pediatricians were uniformly in the habit of recording blood pressures, juvenile malignant hypertension might be recognized earlier. The removal of a hypoplastic kidney before the other kidney has suffered vascular damage seems logical, since unilateral pyelonephritic kidneys causing hypertension have been successfully removed by Butler,<sup>19</sup> Barney and Suby<sup>20</sup> and Barker and Walters.<sup>21</sup> But it must be stated that removal of one ischemic kidney producing a pressor substance may occur at a time when the other kidney has become involved. Thus, in the case of Shirley S. the histologic picture of the large compensatory kidney could not be distinguished from that of the hypoplastic one, it is even possible that such an enlarged kidney is more vulnerable, as Leiter<sup>22</sup> has suggested. If nephrectomies are to be carried out because of unilateral ischemic kidneys, involvement of the other kidney will have to be carefully scrutinized, it may elude the most sensitive tests of renal function at the time. In the case of Shirley S., nephrectomy of the atrophic kidney might have been curative within the first few months after the onset of symptoms, two years before admission to the hospital.

In the fourth case there were so many unusual features that the diagnosis eluded several diagnostic clinics. On admission it became apparent

18 Ask-Upmark, E. Ueber juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, *Acta path et microbiol Scandinav* 6 383, 1929.

19 Butler, A. M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* 16 889, 1937.

20 Barney, J. D., and Suby, H. I. Unilateral Renal Disease with Arterial Hypertension, *New England J Med* 220 774, 1939.

21 Barker, N. W., and Walters, W. Hypertension in Unilateral Renal Disease. *Proc. Staff Meet., Mayo Clin* 15 475, 1940.

22 Leiter, L. Personal communication to the authors.

that there existed (1) quiescent lupus erythematosus, (2) unilateral renal disease with poor excretory function and (3) a major vascular occlusion involving the aorta, at least, at the iliac bifurcation. The combination of lupus erythematosus and renal disease has been well described by Snapper<sup>23</sup> and by Baehr, Klemperer and Schiffrin,<sup>24</sup> the occurrence of endocarditis with lupus has been emphasized by Libman and Sachs,<sup>25</sup> but in this case we suspected a unilateral Goldblatt kidney, which would explain both the renal damage and the pulseless extremities by occlusion of the aorta at the level of the left renal artery. This proved to be the case at operation. In retrospect, a nephrectomy might have been better than the muscle transplant, section of the splanchnic nerve, considered elsewhere, did not seem indicated. Whether death occurred because of a toxemic manifestation of lupus erythematosus or because of a propagating thrombus of the aorta is open to question.

The conditions described in these 4 cases are examples of desperate terminal hypertension. Instead of approaching the surgical treatment of these conditions by section of the splanchnic nerve, the results of which we now have observed up to six years, an attempt was made to graft new circulation on these ischemic kidneys. We cannot say that in the 1 surviving patient the course of the disease has been altered. Our experience, however, serves to emphasize that renal failure is not frequently the cause of death of patients suffering from essential hypertension and that an intravenous pyelogram readily shows differences in size and function of the two kidneys and might demonstrate unilateral renal involvement in the early stages. Nephrectomy at that time, as is shown by cases in the literature, may be curative.

But the majority of patients with essential hypertension show arteriolosclerosis of both kidneys,<sup>26</sup> we have learned this by renal biopsies in the cases of young patients who showed no signs of organic damage and had flexible, moderate hypertension (fig 8). We shall report on a group of patients subjected to splanchnic nerve section in another communication.

Perhaps this surgical exploration of the kidneys of hypertensive patients needs some apology. Certainly no other measure has come to our attention that would alter or arrest the course of hypertension.

23 Snapper, I. Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Mides, S. *The Kidney in Health and Disease*, Philadelphia, Lea & Febiger, 1935, chap. 26, pp. 433-439.

24 Baehr, G., Klemperer, P., and Schiffrin, A. A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, *Tr. A. Am. Physicians* **50** 135, 1935.

25 Libman, E., and Sachs, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Tr. A. Am. Physicians* **38** 46, 1923.

26 Moritz, A. R., and Oldt, M. R. Arteriolar Sclerosis in Hypertension in Nonhypertensive Individuals, *Am. J. Path.* **13** 679, 1937.



If one looks at this disease as a malignant process—and, to be sure, cases of stationary, benign or regressive hypertension in patients below the age of 40 are not frequent—one must attack it with all available means, and not in the terminal stages. More use will have to be made of intravenous pyelograms for hypertensive patients, as they serve for an orientation of the size and function of the two kidneys, later, if the results of the preliminary test suggest it, differential tests of renal function can be carried out. Perirenal insufflation, which we have used in a number of cases to investigate the size of the adrenal glands, is fraught with danger to hypertensive patients, who often have a well developed

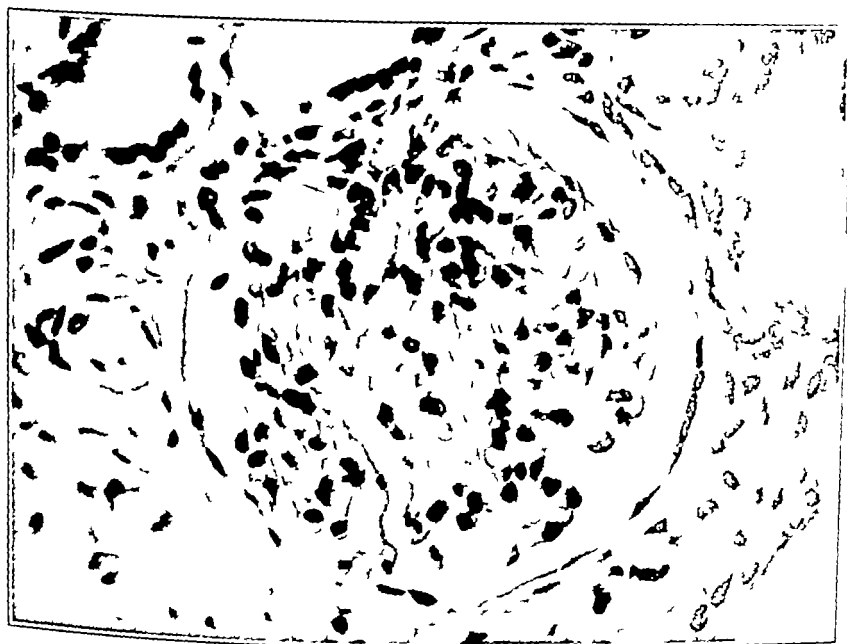


Fig 8.—Renal biopsy specimen from M S, a 24 year old woman in whose case a clinical diagnosis of latent glomerulonephritis was made. The capillary buds are distinct, the epithelium and endothelium show no swelling, the basement membranes do not appear to be thickened, and there is no fibrin deposit.

The afferent and efferent arterioles have rather thin walls and show a small amount of endothelial swelling. The interlobular and arcuate arterioles and small arteries show uniform thickening of this wall, varying in degree and in some instances practically occluding the lumen (diameter of one red cell). The wall is four or five times as thick as the diameter of the red cell.

The convoluted tubules are somewhat disrupted by artefacts, but their nuclei appear normal.

The diagnosis was arteriosclerosis and arteriolosclerosis of the kidney. Note the intact glomerulus and the almost obliterated arteriole to the left.

collateral circulation in the perirenal fat. In the case of Edith H (not reported here), a 29 year old unmarried woman in whose case the diagnosis of malignant nephrosclerosis was made, the right kidney was

outlined without difficulty, but not enough air was visible on the left side (fig 9). After the perirenal injection on the left side, she had a severe reaction, which was due to a large perirenal hematoma, there was a huge amount of clotted and unclotted blood around the kidney and under the capsule, as was demonstrated later on exploration.

The results in our cases do not answer the question whether renal revascularization is of any value for patients suffering from nephrosclerosis, nor is it positively known that certain patients with chronic glomerulonephritis or pyelonephritis, who may undoubtedly have end-arteritis obliterans in the afferent and glomerular vessels, would not be



Fig 9—Perirenal insufflation of 250 cc of air in the case of E. H. Only the right side was visualized. The film was taken twenty-five hours after injection. Note the triangular shadow above the upper pole of the kidney, representing a normal-sized right adrenal gland.

equally suitable for such a procedure. A combination of renal sympathectomy with decapsulation has recently been advocated by Chabamier and his associates.<sup>27</sup> These authors correctly pointed out that hypertension with nephritic symptoms may be due to malignant nephrosclerosis with glomerular manifestations or to chronic diffuse glomerulonephritis.

<sup>27</sup> Chabamier, H., Gaume, P., and Lobo-Onell, C. *Vue d'ensemble des résultats d'interventions pratiquées dans quarante-neuf cas de néphroangiosclérose.* Presse med. 46 1818, 1938.

nephritis with secondary vascular changes. The result in both instances is the ischemic kidney, when unilateral, it can be removed, but this certainly does not apply to the majority of diffuse renal diseases. The greatest stumbling block to effective vascularization of an arteriosclerotic kidney is that the vascular obstruction is terminal, this type of arteriolar destruction is the most difficult to treat in the extremities. Nevertheless, an extraglomerular circulation, affecting perhaps the tubules,<sup>27a</sup> might still be of some use. We have put these cases on record to report the futility of this procedure in the late stages. We believe that revascularization should not be abandoned until it is evaluated by trial on patients with early benign nephrosclerosis giving the typical clinical picture of essential hypertension.

Finally, attention should be called to the frequent occurrence of partial obstruction of the main renal artery in association with "essential" hypertension in man. For kidneys with such obstruction which were studied as postmortem material by Blackman,<sup>28</sup> surgical procedures to increase the blood flow in the terminal vascular bed offer more promise.

#### SUMMARY

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated, the cortex was incised and the omentum or a pedicled muscle flap was wrapped around the kidney. The 4 case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

122 South Michigan Avenue

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27a A study of the architecture of the kidney in chronic renal disease (Oliver, J. Architecture of the Kidney in Chronic Bright's Disease, New York, Paul B Hoeber, Inc, 1939) reveals the striking hypertrophy and hyperplasia of the proximal convoluted tubules in aglomerular nephrons, a phenomenon of repair.

28 Blackman, S S, Jr. Arteriosclerosis and Partial Obstruction of Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull Johns Hopkins Hosp 65 353, 1939

# SUTURE STUDIES

## A NEW SUTURE

JOSEPH E BELLAS, MD

PEORIA, ILL

A profound and exhaustive study of wound healing appears in an article by Arey,<sup>1</sup> which should be informative and illuminating to all students of surgery. This study was conducted without reference to the presence of sutures and stands virtually as a control for any study on wound healing complicated by additional influences. Thus a study of wound healing as influenced by sutures is of paramount importance from the standpoint of fundamental and practical application.

The controversy concerning absorbable and nonabsorbable sutures has been fluctuating ever since Halsted<sup>2</sup> broke away from the precedent of absorbable sutures to advocate the use of silk sutures.

In recent years the subject has interested me very much. In my experiences with various sutures, such as plain, chromic, tanned and iodized catgut and silk, linen, steel wire and artificial sutures, I have felt that the controversy concerning the relative merits of absorbable and nonabsorbable sutures is leading nowhere. I have become convinced that the emphasis in discussing sutures should be directed to whether a given suture is reacting or nonreacting.

From extensive clinical and experimental work I have tried to ascertain what factors exist in sutures in current use to make them react and have studied various sutures in the light of these factors.

I have enumerated five principal factors in the production of a reacting effect:

- 1 Absorbability of a suture
- 2 Favorable bacterial medium from the split products of a suture
- 3 Allergic sensitivity of tissues to foreign proteins in a suture
- 4 Susceptibility of a suture to enzymatic digestion
- 5 Capillary retention of stagnant serum within the body of a suture

1 The more absorbable a suture is, the more soluble material there will be to diffuse out into the tissues and arouse an irritating response. In addition to this, the more soluble a suture is, the greater is the

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From the Surgical Service of the Collins Clinic

1 Arey, L. Wound Healing, *Physiol Rev* **16** 327-406, 1936

2 Halsted, W S. Ligature and Suture Material, *J A M A* **60** 1112-1113 (April 12) 1913

depreciation in certain of its physical properties, such as tensile strength and knot holding<sup>3</sup>

2 The split products resulting from the breaking down of a suture of animal origin will offer an excellent culture medium for bacterial growth and will thus increase and extend the zone of injurious reaction. Inherent contamination of such a suture, which sometimes occurs with catgut, will yield an immediate pathogenic agent which will further aggravate this reaction<sup>4</sup>

3 Allergic reaction from sensitivity of the tissues to the foreign proteins in the original suture or to its broken-down products has been observed too often to allow doubt of its injurious effect in delaying or impairing primary repair<sup>5</sup>

4 A suture of animal origin or of protein composition lends itself in varying degrees to digestion by the trypsin-like enzymes ever present in the body tissues. The effect of this and of its aftermath gives rise to varying degrees of irritating response<sup>6</sup>

5 The infiltration of serum or body fluids within the body of a suture by capillary attraction gives rise to stagnation of serum. This acts as a favorable culture medium for bacterial growth and leads to an inflammatory reaction within the suture and to extension of infection along the course of the suture.

The observation that any one or more of these factors inherent in a suture make that suture an inherently reacting one is a conclusion inevitably reached from a close study of suture reactions. Thus, catgut

3 Howes, E L, and Harvey, S C. Strength of Healing Wound in Relation to Holding Strength of Catgut Suture, *New England J Med* **200** 1285-1291, 1929. Jenkins, H P. Clinical Study of Catgut in Relation to Abdominal Wound Disruption, *Surg, Gynec & Obst* **64** 648-662, 1937. Rhoads, J E, Hottenstein, H F, and Hudson, I F. Decline in Strength of Catgut After Exposure to Living Tissues, *Arch Surg* **34** 377-397 (March) 1937.

4 Meleney, F L, and Chatfield, M. How Can We Insure Sterility of Catgut? *Surg, Gynec & Obst* **50** 271-277, 1930. Clock, R O. Bacterial Species Found in Non-Sterile Surgical Catgut Sutures, *ibid.* **66** 878-881, 1938.

5 Babcock, W W. Catgut Allergy, with a Note on the Use of Alloy Steel Wire for Sutures and Ligatures, *Am J Surg* **27** 67-70, 1935. Hinton, J W. Allergy as an Explanation of Dehiscence of Wound and Incisional Hernia, *Arch. Surg* **33** 197-209 (Aug) 1936. Kraissl, C J, Kesten, B M, and Ciumotti, J G. Relation of Catgut Sensitivity to Wound Healing, *Surg, Gynec. & Obst* **66** 628-635, 1938.

6 Allen, J C B. The Fetish of Catgut, *M J Australia* **2** 150-151, 1934. Reil, H. The Catgut Problem, *Chirurg* **4** 17-23, 1932. Kraissl, C J, and Meleney, F L. A Method for Determining the Time of Catgut Digestion in Vitro, *Surg, Gynec & Obst* **59** 161, 1934.

reacts because of factors 1 to 4 inclusive. Natural silk reacts because of factors 4 and 5.<sup>7</sup> The treated silks, linen and rayon in current use react because of factor 5.

Hence all absorbable sutures and all reacting nonabsorbable sutures, by virtue of their irritating effect, would be expected to oppose primary physiologic repair.

It is an extremely significant observation that all the sutures in current use fall into the group of reacting foreign bodies. With a knowledge of this fact, it becomes readily comprehensible why dissatisfaction with these sutures has often been expressed.

There is a general conviction among physicians and surgeons alike that introduction of foreign bodies into the tissues inevitably gives rise to an unfavorable foreign body reaction, with the development of inflammatory cells, macrophages and giant cells and ultimately of a thick wall of fibrous tissue to wall off the foreign body.

It has been my observation that this contention is untrue and fraught with the liability of false conclusions. If the factor of pure mechanical irritation is eliminated, no one who has studied the behavior of foreign bodies, such as rustless steel wire, vitallium screws and glass, will deny that these foreign bodies are nonreacting within the tissues. Thus it is essential that in the consideration of sutures emphatic differentiation be made between reacting and nonreacting foreign bodies.

It was my endeavor to find a nonreacting foreign body which could be utilized as a suture that led me to the search for a nonreacting suture. In order to achieve the attainment of an ideal suture I postulated the requirements that seemed essential in such a suture. These are

1 The suture should be sterilizable by common hospital and office methods, that is, by autoclaving and by boiling, without significant loss of desirable properties.

2 The suture should possess pliability, satisfactory tensile strength, knot-holding qualities and uniformity for given sizes.

3 The suture should be nonreacting or relatively nonreacting in the body tissues.

4 It should be insusceptible to the action of tryptic enzymes in the body tissues.

5 It should be insusceptible to the chemical and physiologic agents in the body tissues.

6 It should be unaffected by bacteria and incapable of promoting the growth of bacteria.

7 Starlinger, F. The Later Fate and the Clinical Effect of Silk in the Wall of Gastro-Intestinal Fistulae, *Zentralbl f Chir* 54:250, 251, 1927.  
Donaldson, J. K., and Cameron, R. R. Study of Use of Silk, Catgut, and Noble Plication with Reference to Abdominal Adhesions, *Surgery* 5:511, 1913.

- 7 It should be incapable of retarding the process of repair
- 8 It should be incapable of inducing disturbing edema or of inducing effusion of tissue fluids in operative wounds
- 9 It should be incapable of inducing allergic reaction and, incidentally, of inducing toxic or carcinogenic influences
- 10 It should be practically unaffected by clinical ranges of heat and moisture
- 11 It should be *truly* noncapillary
- 12 It should permit ease in handling, at least equal to that of catgut
- 13 It should be radiolucent

The logical conclusion that arises from the foregoing requirements leads to the final requirement

- 14 It should be nonabsorbable

A study of present day sutures discloses the significant fact that none are available thus far that incorporate all of the properties just enumerated. The rustless steel alloy wire of Babcock and Kurlander<sup>8</sup> makes the closest approach. Its radiopacity and difficulty of surgical manipulability militate against its general use as a universal suture.

A type of suture which consists of silk wound around a core of steel wire has been described.<sup>9</sup> I have not used it but it may be assumed that it combines the disadvantages of silk and those of wire.

An attempt has been made to stain and adapt a new fiber called nylon<sup>10</sup> as a surgical suture. Little can be said as yet with regard to its utility. I have seen but one photomicrograph, which, taken at two days, was shown in contrast to a photomicrograph of an intense silk suture reaction at eight days but which itself showed a moderate inflammatory reaction at this early date. Moreover, monofilic nylon fails signally in one of the essential physical properties, that of knot holding, whereas the suture composed of multiple filaments may be expected to react much like the silk suture. However, it must be stated that the manufacturers have taken the precaution of recommending it only as a removable superficial suture.

The development of my new plastic suture is the result of a three year search for a nonreacting suture that attempts to combine all of the requirements enumerated. That objective has apparently now been attained, and after extensive experimental and personal clinical trial I have finally reached the point where I can, with confidence, introduce my improved suture, based on a new principle of nonreaction-plastigut.

<sup>8</sup> Babcock, W. W. Ligatures and Sutures of Alloy Steel Wire, *J. A. M. A.* **102** 1756 (May 26) 1934. Kurlander, J. J. Rustless Steel Wire. A New Addition to the Surgeon's Armamentarium, *J. Bone & Joint Surg.* **12** 191, 1930.

<sup>9</sup> Rau, O. Experiences with the Modern Suture Material Medrafil," *Zentralbl. f. Chir.* **64** 509, 1937.

<sup>10</sup> Ziegler, P. F. Du Pont Nylon Steps into Surgery, *Du Pont Mag.* **33** 14-15, 1939.

Plastigut<sup>11</sup> is a nonreacting, nonabsorbable, noncapillary suture in which the essential components are synthetic plastics. These plastics are polymerized condensation products of aliphatic and aromatic alcohols with short chain aliphatic aldehydes. They may be considered analogous to bakelite, lucite and vinylite. The appearance of the suture is similar to that of catgut, and it is prepared in equivalent sizes, but from that point on the similarity ceases.

Animal experimentation was resorted to in order to study the effect of various sutures in relation to tissue reaction and to the process of wound healing as ascertained by microscopic studies. Plain and chromic catgut, natural and treated silks, natural and Pagenstecher linen and plastigut were embedded deeply in the tissues of guinea pigs and dogs, and at intervals between two days and six months the animals were killed and sections made of the various sutures. All the aforementioned sutures were buried in the same animal for many of the specified periods so as to have identical conditions. A large number of microscopic sections were thus obtained, of which the accompanying photomicrographs demonstrate the typical results.

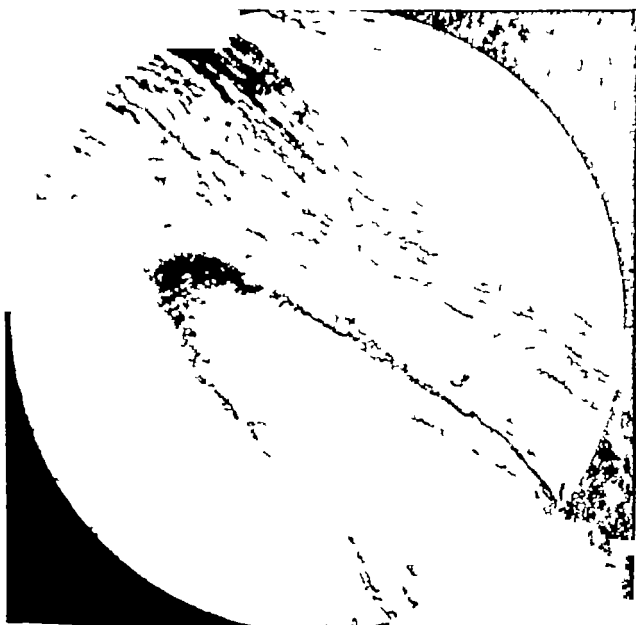
To the practical surgeon, clinical trial is the most crucial test, and my own interest and curiosity led me to use plastigut in a few operative cases. The prompt healing and absence of reaction, as well as a definite reduction in the amount of pain from the incision in "clean cases" so gratified me that I was encouraged to use plastigut in an ever increasing percentage of cases until I found myself using it as the routine suture. My subsequent experience has only convinced me further of the value and range of utility of the suture. Another factor of economic importance is the shortened period of hospitalization which results from its use. It was obvious that the stage of repair in cases in which plastigut was used was far more advanced at any given day than in cases in which catgut was used, because there was no irritating inflammatory and exudative reaction to prevent or hinder repair. Subsequent post-operative incisional hernias suddenly became a rarity. Even vesicovaginal fistulas, which had formerly been a specter and a nightmare because of repeated recurrences, miraculously healed as by primary intention. It became increasingly apparent to me that when catgut was used the incisions eventually healed not because of but in spite of the catgut.

I have used plastigut in about 600 cases, but sufficient time has elapsed to give the ultimate results in only 406 cases. These represent an experience over a three year period in all types of cases, under all manner of conditions and with varied technics. I have learned a great many things about sutures in carrying out this work, particularly in relation to the use of plastigut. At first my sutures were crude and

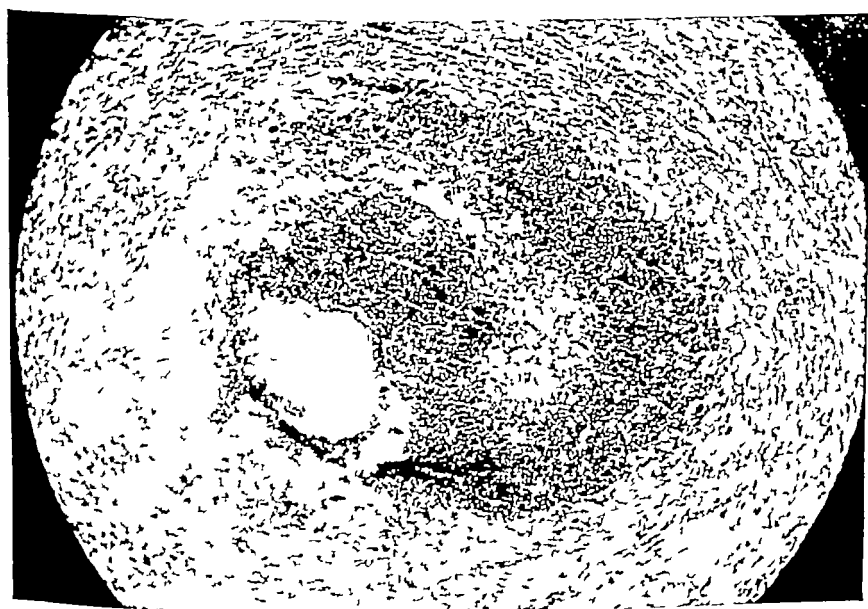
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<sup>11</sup> This name has been adopted for convenience and simplicity.





A

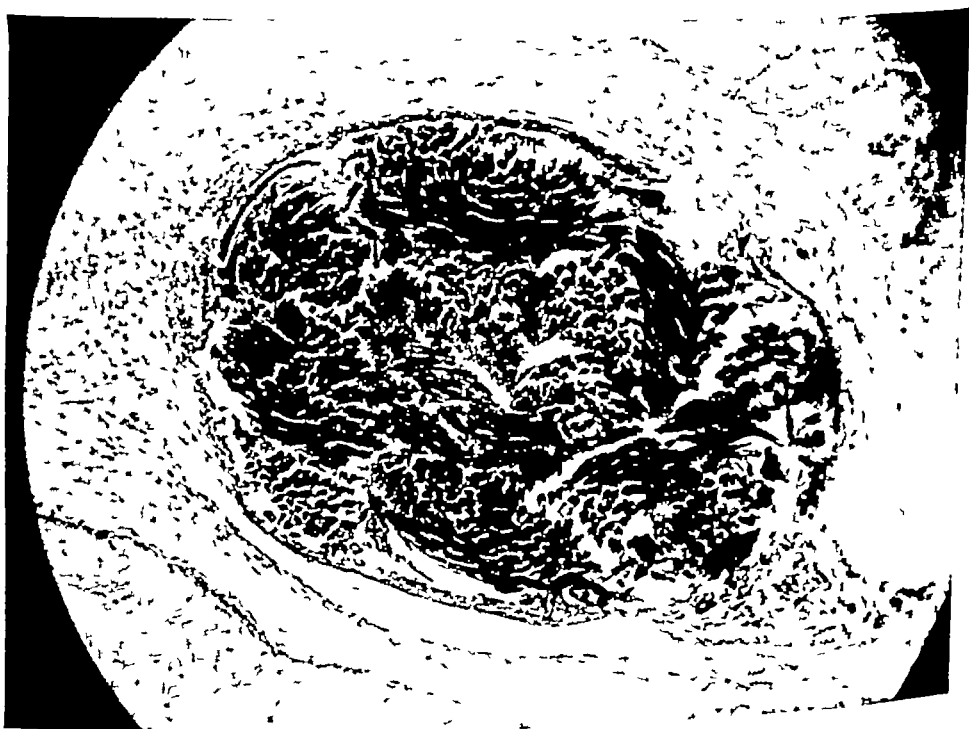


B

Fig 1—*A*, chromic catgut suture at the end of five days. The catgut suture is beginning to be absorbed. An inflammatory reaction is present especially at the site of absorption. *B*, section at two weeks, in which a plain catgut suture is almost completely digested and replaced by a wide, rounded area filled with acute inflammatory cells and showing central necrosis. This is virtually an acute abscess. The photomicrographs are typical of the reactions with catgut.

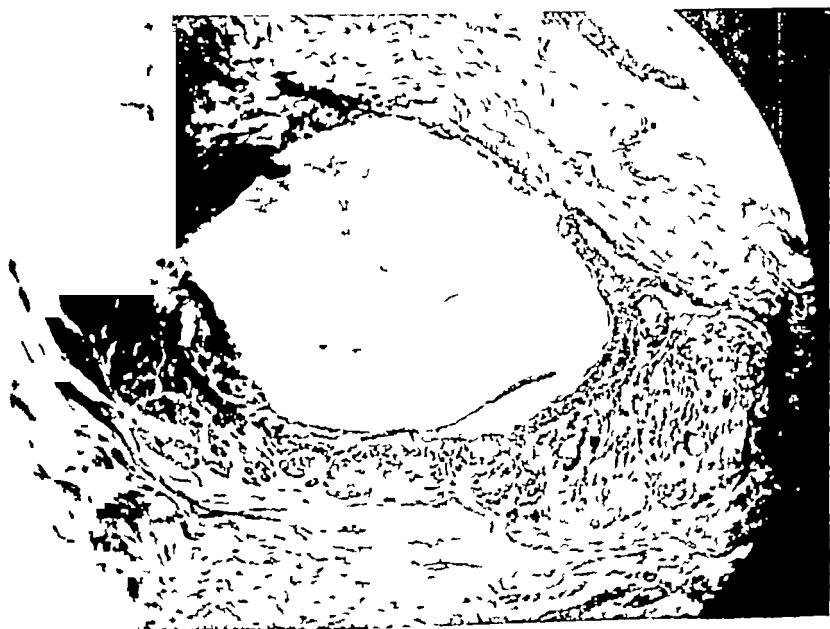


A

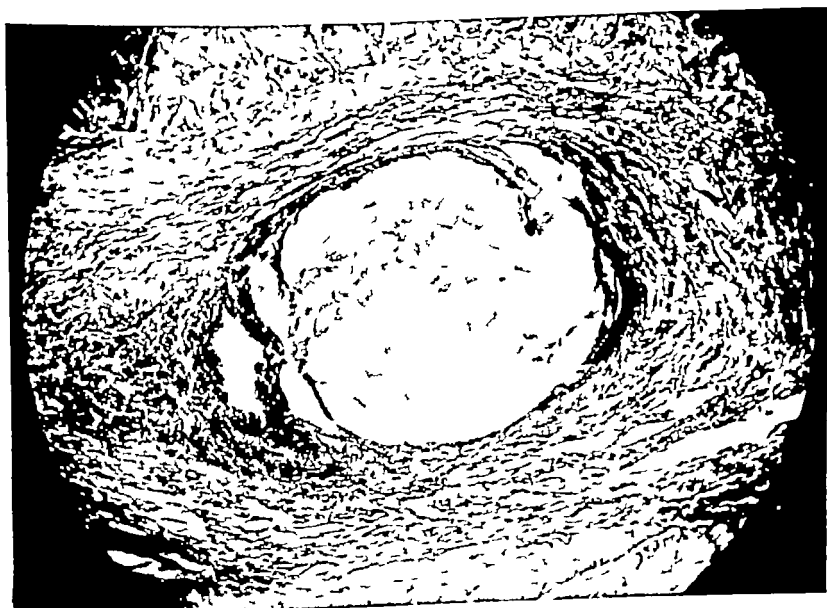


B

Fig 2—*A*, typical section of a silk suture claiming to be noncapillary and serum proof. At seven days a marked infiltration of inflammatory cells and serum can be seen between the fibers of silk. This shows definitely how capillarity favors the retention and promotion of infection. *B*, section at four weeks of another type of silk suture claiming to be serum proof and noncapillary. Note the presence of inflammatory cells within the structure of the suture and between the fibers.

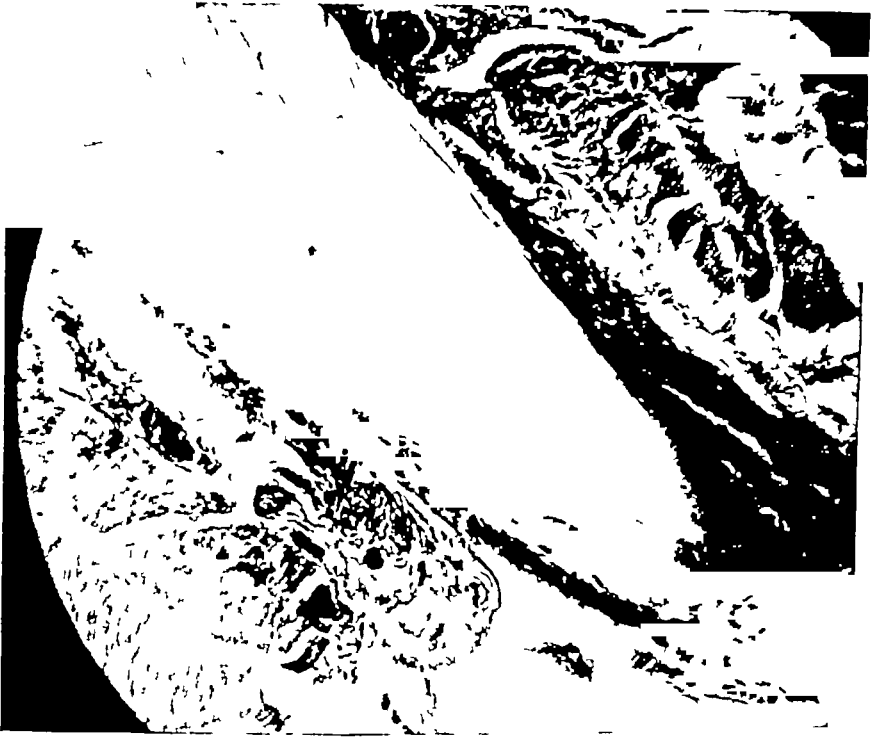


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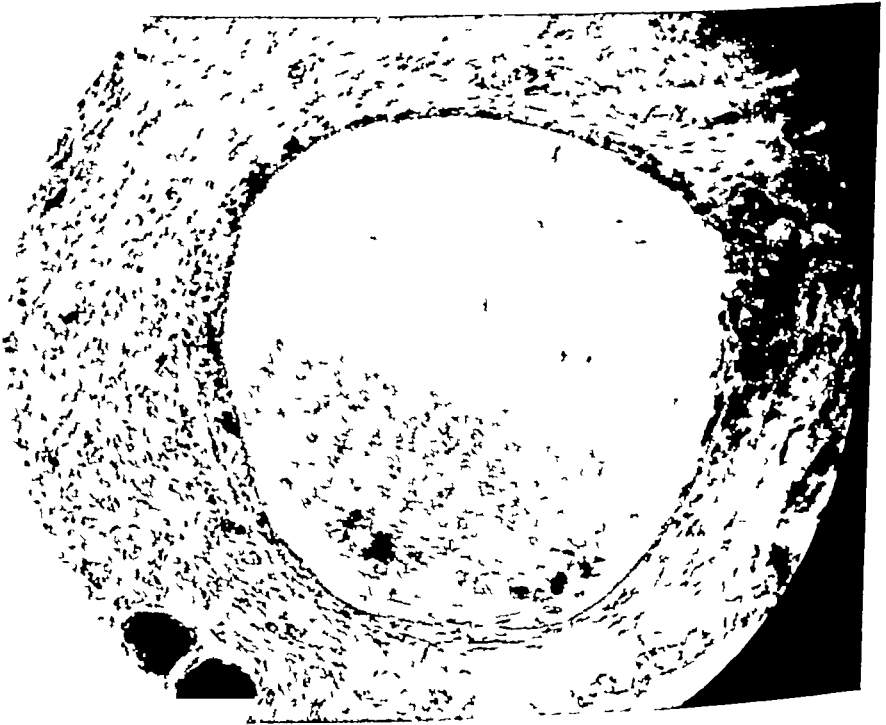


B

Fig 3—*A*, section of plastigut at seven days showing the suture surrounded by normal tissue, with no evidence of inflammation in or around the suture *B*, section of plastigut at two weeks. There is no reaction, no inflammation and no capillarity

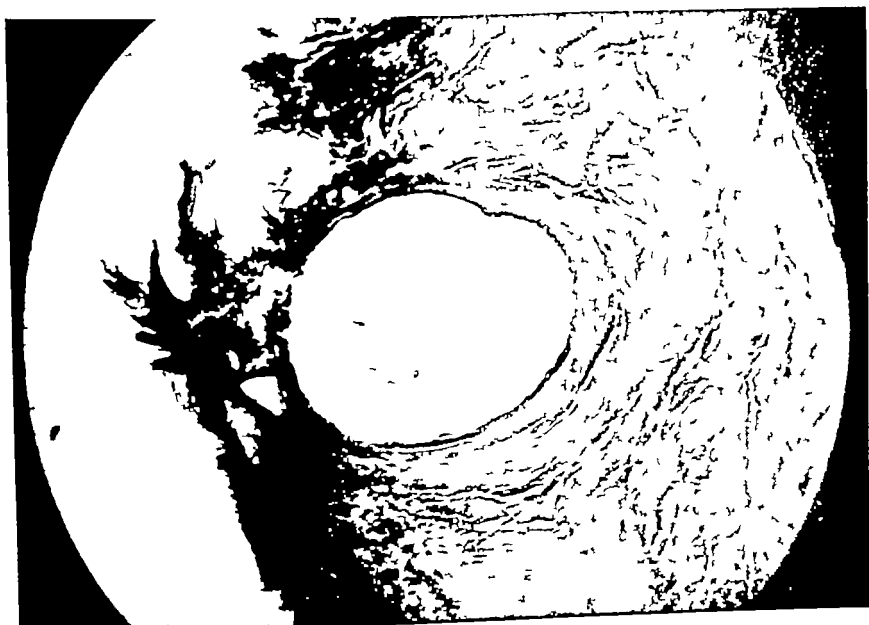


A

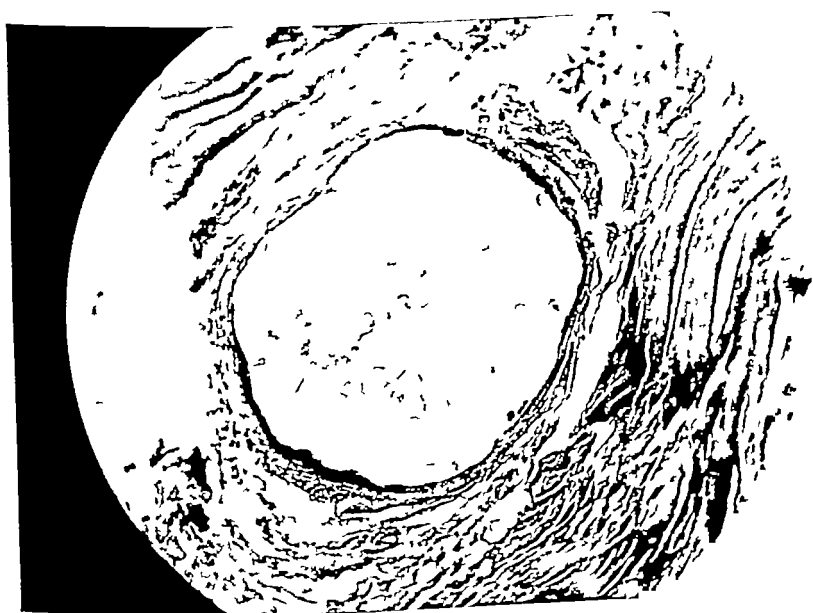


B

Fig 4—*A*, section of plastigut six weeks after exposure to an infected field. The guinea pig chewed off its skin suture, and the incision had to be resutured with wire the next day. The infection which resulted has now subsided, and the suture has healed in. In spite of the marked infection around the suture there has been no tendency whatever for inflammatory invasion into the suture. There is no capillarity. *B*, section of plastigut at six months. There is no reaction, no inflammation and no capillarity.



A



B

Fig 5—*A*, plastigut at one year in a human being. There is no retained infection within the suture from capillarity and no evidence of infection is present in the surrounding tissues. This demonstrates positively that the suture remains a nonreacting foreign body without adversely affecting the surrounding normal tissues. *B*, plastigut after two years and three months in a human being. No inflammatory reaction and no capillarity can be observed. This confirms once more the nonreacting character of the suture.

large I frequently used the equivalent of no 2 double as a continuous suture, both in clean and in infected wounds. Of 335 clean wounds, 7 showed localized reactions from mechanical irritation, and some of these required a secondary procedure to remove the cause of the irritation.

These figures require further clarification in relation to changing technic (see table).

It is obvious that the technic in the second group (use of fine sizes and single thread) has eliminated mechanical irritation almost to the point of extinction in clean wounds and has materially reduced "stitch trouble" in infected or contaminated wounds. I am convinced that this mechanical irritation arises from sutures of large bulk and from large knots. All others healed by first intention and have apparently remained healed. Since I have adopted single threads and small sizes up to size 0, whether continuous or interrupted, healing has been primary in all but 1 case.

*Results with Plastigut*

	Clean Wounds	Stitch or Sinus Trouble	Percentage	Infected or Contaminated Wounds	Stitch or Sinus Trouble	Percentage
First Group Continuous no 2 plastigut, double or single	105	6	5.7	21	10	47.6
Second Group Continuous or interrupted no 0000 to no 0 plastigut, single	230	1	0.435	50	9	18.00

In a three year experience with plastigut I have encountered about all the complications that are possible with the suture. I have studiously tried to analyze my experiences and am now convinced that a certain technic should accompany its use. I am impressed by one observation—that continuous sutures within the peritoneal cavity can be used with impunity. I have observed no intraperitoneal complications following use of the continuous suture in either clean or infected wounds. There are no objections, however, to the use of interrupted intraperitoneal sutures. For clean wounds, extraperitoneal sutures may be continuous or interrupted. Generally speaking, interrupted sutures are preferable. The incisions heal promptly by primary intention, with no evidence of reaction, and the skin and underlying tissues during the period of healing remain pliable. For infected wounds and in cases of drainage interrupted suture technic is compulsory for extraperitoneal location. I am convinced that the advocates of the Halsted silk technic will now find an almost ideal material in plastigut. In infected wounds, there is a definite tendency for the infection to localize without the spreading infection I so frequently observed with catgut. The inter-

rupted loops of plastigut will become loosened when uprooted by a slough and in most cases will be cast off with the slough. Occasionally it may be necessary to use a hook for a loop that has become loosened but not cast off. Those sutures which have become buried in viable tissues remain buried and cause no trouble. I am convinced that no sizes above no 0 or, at most, no 1 should be used and that all strands should be used single. The most useful range of sizes in my work has been between no 0000 and no 00. The strands are tough, they have a substantial "feel" equal to that of catgut and superior to the limpness of fine silk. Those who are advocates of the Halsted silk technic will find an improved substitute in a relatively heavier, relatively stronger, nonreacting, nonabsorbable suture that has all the advantages of silk without its disadvantages.

During the period of its development plastigut was supplied to a limited number of well known surgeons for clinical trial. All responses to a questionnaire after clinical trial were eminently and unanimously favorable to plastigut.

My convictions are based primarily on clinical application and results and are further supported by considerable experimental and microscopic evidence of the general utility and nonreacting qualities of the new suture.

#### SUMMARY

The choice of a suture should depend on a study of clinical and microscopic effects on wound healing.

Sutures should be classified as reacting and nonreacting.

Five principal factors have been enumerated in the production of a reacting effect. In the light of this study, all sutures in current use are inherently reacting foreign bodies.

A nonreacting foreign body will induce little or no inflammatory or irritating reaction.

The ideal properties in a suture are postulated.

Plastigut, a new suture, closely incorporates the ideal properties of a universal suture.

Plastigut is a nonreacting, nonabsorbable, noncapillary suture in which the essential components are synthetic plastics.

Extensive experimental and clinical studies have, in my opinion and in that of others, verified the claims for plastigut.

The technic with plastigut is described.

Plastigut represents a suture based on a newly emphasized principle of a nonreacting foreign body.

Plastigut is obtainable from the Plastigut Foundation, 428 Jefferson Building, Peoria, Ill.

The original work was performed in collaboration with Dr. Andrew C. Ivy, Professor of Physiology, Northwestern University.

# RECURRENCE OF INFECTION AFTER ELECTIVE OPERATIONS IN CASES OF HEALED SUPPURATION IN BONES AND JOINTS

J B DAVIS, M D

PORTLAND, ORE

Elective operative procedures in cases of healed suppuration in bones and joints are frequent in the practice of the orthopedic surgeon. The frequency with which osteomyelitis or suppurative arthritis recurs as a result of common, everyday trauma is only too well known. Operative trauma, such as that associated with arthrodesis, arthroplasty or osteotomy, is little different from closed external trauma. One should, therefore, expect some recurrence of infection in healed suppurative lesions of bones and joints in the event of operation. Actually, such recurrent infection has been observed for a number of years, and the frequency with which suppuration recurs was the impetus for this analysis. According to Wilensky,<sup>1</sup> destruction of trabeculae and subsequent hemorrhagic exudate result in an area of decreased resistance that can readily become infected with any available bacteria. The latency of osseous infection is a common disturbing factor, and there are frequently available bacteria in the operative area to produce the recurrent infection. Fraser<sup>2</sup> and others have cited instances of long delayed recurrence of infection. In 1 case a bone abscess remained closed for thirty-eight years. I have observed 1 case in which a closed bone abscess remained quiescent for four years and was discovered only during an elective osteotomy.

The material contained in this report was obtained from the service of Dr Arthur Steindler, of the University of Iowa. The series analyzed consists of all the operations on healed suppurative areas in bones and joints that have been done in this clinic up to January 1940. A total of 215 operations was reviewed and serves as a basis for the conclusions to be drawn from this analysis. These procedures are divided first, into an etiologic classification consisting of (1) operations for gonorrheal arthritis, (2) operations for suppurative arthritis, (3) operations for hematogenous osteomyelitis, and (4) operations for

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From the Department of Orthopedic Surgery (service of Dr A Steindler) the State University of Iowa Hospitals

<sup>1</sup> Wilensky, A O Osteomyelitis, New York, The Macmillan Company 1934

<sup>2</sup> Fraser, J Acute Osteomyelitis, Brit. M J 2 605-610 (Oct. 4) 1924



traumatic osteomyelitis Suppurative arthritis needs a little defining in that under this heading are included only cases of articular involvement in which there was no osseous involvement It is classified in this way because suppurative arthritis with regional osteomyelitis has all the characteristics of regular osteomyelitis Likewise, the term traumatic osteomyelitis needs to be clarified, since under this heading are included only those cases in which the infection resulted from compound wounds of bone

The cases were next divided into two classes depending on whether operation was performed immediately through the area of the previous suppuration or near it but not through it This distinction is of considerable importance, as will be shown later No attempt was made to correlate the type of operation with the recurrence of infection, since no case was accepted for analysis in which the operation did not constitute a major traumatic event to the bone The most common procedures were arthroplasty, arthrodesis, osteotomy and bone graft The cases were investigated from the standpoint of duration of activity of the infectious process, number of years the infectious process had been quiescent, age, sex, roentgen appearance and bacteria when available

#### GONORRHEAL ARTHRITIS

This condition is included in this analysis because it is on occasion associated with frank suppuration in joints and because the causative organism is a notoriously good pus producer in other locations The

TABLE 1—*Gonorrheal Arthritis*

Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent	Recurrence
26	0 1 1 5	0 0	0 5-14	3.2	None

patients were 7 men and 20 women Twenty-seven cases were reviewed The location of the process was as follows knee, 14 cases, hip, 3 cases, hand, 1 case, elbow, 6 cases, foot, 3 cases One patient in this group had a typical postoperative wound infection with *Staphylococcus albus*, but as such it did not represent a recurrence of the original infection All the operations were done directly into the old healed articular areas, and all included work on bone, yet, in spite of this and the fact that in some instances the areas had been healed for only six months, there still were no recurrences of infection From this series it would appear that healed gonorrheal joints can be operated on with little, if any, danger of recurrence and at almost any time the operator desires

## SUPPURATIVE ARTHRITIS

This group includes all cases of healed purulent articular infection without associated osteomyelitis. Eighty-three cases were reviewed, and in 48 instances the operation was performed through the previously involved joint, while in 35 instances the operation was performed near but not through the previously involved joint.

The statistics on the exactly located operations, after which infection did not recur, are as follows: cases, 42, male patients, 18, female patients, 24. Location: knee, 24 cases, hip, 12 cases, elbow, 6 cases.

The statistics on the exactly located operations after which infection did recur are as follows: cases, 6, male patients, 4, female patients, 2. Location: hips, 3 cases, knee, 3 cases.

TABLE 2—*Nonrecurrent Suppurative Arthritis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
3-40	21.7	0-14	0.6	0.5-24	4

TABLE 3—*Recurrent Suppurative Arthritis in Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
17-60	30	0-11	0.6	1-30	Over 11

There is little difference between the general statistics in these two series. The quiescent period was longer in cases of recurrent than in those of nonrecurrent infection. This bears out the contention that the time of quiescence is not the important factor in recurrence of infection in healed suppurative arthritis when it is operated on. This fact has been previously pointed out by Steindler.<sup>3</sup> The contrast of the 6 cases of recurrence to the total of 48 cases gives a recurrence rate of 13 per cent. The recurrent bacterium in this series was the staphylococcus in all but 1 case, in which it was the streptococcus. The duration of the recurrent infection varied from three-tenths year to eleven years, with an average of three and five-tenths years. This, then, constitutes a complication to be avoided when possible. The percentage of recurrence in this series corresponds closely to that reported by Hallock<sup>4</sup> or 2

3 Steindler, A. *Orthopedic Operations*, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

4 Hallock, H. *Study and End Results of Seventy Arthroplasties and Reconstruction Operations on Hip Joint*, Surg., Gynec. & Obst. 68:106-112 (Jan.) 1939.

cases in 20 operations, in 1 of these the infection had been quiescent for five years and showed a Staph aureus on culture at the time of operation

The statistics on operations done, near healed suppurative joints in which the infection did not recur are as follows cases, 32, male patients, 23, female patients, 9 Location hips, 23 cases, knee, 9 cases

TABLE 4—Nonrecurrent Suppurative Arthritis Near Operative Area

Age, Years	Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
3-47	32	0 1 10	2	0 4 30	15

TABLE 5—Recurrent Suppurative Arthritis Near Operative Area

Age Years	Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
13-18	16	0 8 3	1 4	1 15	6

TABLE 6—Nonrecurrent Hematogenous Osteomyelitis in Operative Area

Age, Years	Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
1.5-47	16	0 2 5	1	1 30	6 4

TABLE 7—Recurrent Hematogenous Osteomyelitis in Operative Area

Age Years	Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
10-51	21	0 1 0	1.5	1 9	2 5

The statistics on operations done near to healed suppurative joints in which the infection did recur are as follows cases, 3, male patients, 2, female patients, 1 Location hips in all cases

The percentage of recurrence of infection in these suppurative joints operated on near but not through the previous involved area is, then, 8 per cent The time required for the secondary healing varied from three-tenths year to one year This group of operations performed near areas of previous infection, contrasted to the exactly located operations, shows a slightly less frequency of recurrence but a much shorter period of secondary healing time

## HEMATOGENOUS OSTEOMYELITIS

Seventy-six operations were analyzed in this group, of these, 35 were performed in the previously involved area and as such are classified as exactly located operations, while 41 were performed near the involved area but not through it and as such are classified as neighboring operations

The statistics on the exactly located operations after which the infection did not recur are cases, 19, male patients, 12, female patients, 7 Location hip, 9 cases, knee, 4 cases, tibia, 3 cases, femur, 1 case, wrist, 1 case, tarsus, 1 case

The statistics on the exactly located operations after which the infection did recur are cases, 16, male patients, 7, female patients, 9 Location hip, 6 cases, knee, 3 cases, tibia, 3 cases, femur, 2 cases, ankle, 1 case, astragalus, 1 case

The analysis of these two sets of statistics shows little variance The quiescent period was longer in cases of recurrent than in cases of non-

TABLE 8—*Nonrecurrent Hematogenous Osteomyelitis Near Operative Area*

Age, Years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
2-48	18	0 1-14	2	0 5-33	5

recurrent infection, but there were periods as long as nine years of quiescence followed by recurrence, which again bears out the contention that time alone cannot be used as a criterion for elective operative intervention in cases of healed osteomyelitis The recurrences were again preponderantly staphylococcic, with only 1 instance of streptococcic infection The recurrent complications lasted from two-tenths year to twelve years, with an average of two and nine-tenths years The contrast of these two groups gives a rate of recurrence of infection of 46 per cent for operations at the site of previously healed osteomyelitis

The statistics on the operations done near areas of healed osteomyelitis that did not recur are cases, 40, male patients, 17, female patients, 23 Location hip, 33 cases, tibia, 3 cases, knee, 3 cases, tarsus, 1 case

There was only 1 case of recurrence in the operations performed in a neighboring area of this group, and this occurred in a 39 year old man The infection had been active for twenty years and quiescent for six months, it recurred for eighteen months Contrasting this 1 case with the 40 cases in which infection did not recur shows a recurrence of 2.5 per cent This is in marked contrast to 46 per cent of recurrence when the operation was carried out through the previously involved

area. Steindler has previously called attention to this low frequency of recurrence of osteomyelitis when the operation is carried out away from the area of healed osteomyelitis

#### TRAUMATIC OSTEOMYELITIS

In all of the cases in this group operation was done through the previously osteomyelitic area and so fall into two groups first, those in which the infection recurred and, second, those in which it did not

First group (recurrences) cases, 8, male patients, 6, female patients, 2 Location tibia, 6 cases, ankle, 1 case, femur, 1 case

Second group (nonrecurrent infections) cases, 21, male patients, 14, female patients, 7 Location forearm, 8 cases, tibia, 7 cases, humerus, 4 cases, tarsus, 1 case, fibula, 1 case

TABLE 9—*Recurrent Traumatic Osteomyelitis in Operative Area*

Age, Years	Average Age Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
5-3	28	0.2-4	1.2	0.4-9	2.4

TABLE 10—*Nonrecurrent Traumatic Osteomyelitis in Operative Area*

Age years	Average Age, Years	Years Process Active	Average Years Process Active	Years Process Quiescent	Average Years Process Quiescent
6-3	24	0.3-4	1.1	0.4-16	3.5

The contrast of these two groups shows little variance in the general statistics. There was a 28 per cent recurrence of infection. The secondary recurrent complication lasted from three-tenths year to six years, with an average of two years. Here, as in the previous groups, the time of quiescence is not related to the recurrence. This has been emphasized by Watson-Jones,<sup>5</sup> who recommended a six month quiescent period before operation.

#### ROENTGEN APPEARANCE

Roentgenograms were investigated in an effort to determine criteria that would indicate recurrence of infection in the event of operative trauma at the site of previous suppuration in bones and joints. When all of the cases in which bone was involved were removed from the group of cases of suppurative arthritis, there was a group of 11 cases of true suppurative arthritis in which there was roentgen evidence of suppura-

<sup>5</sup> Watson-Jones, R. *Fractures and Other Bone and Joint Injuries*, Baltimore, Williams & Wilkins Company, 1940

tion confined to the joints alone and in which there was no recurrent infection. Figure 1 shows an example of this condition. This is in harmony with the finding of the low percentage of recurrence of infection in cases of suppurative arthritis in the general statistics. The discrepancy between the number of cases studied by roentgenograms and those studied by case histories is due to the fact that the roentgenograms were available for only ten years, while the histories were available for twenty-five.



Fig 1—Roentgenogram in a case of pure suppurative arthritis. There is no evidence of involvement of bone, and all destruction has been confined to the joint.

The most imminent problem concerns the decision as to when to operate on an area of healed osteomyelitis. There are a number of roentgen findings that are evidence of infectious involvement of bone. Obviously, no cases were seen in this group of osteomyelitis in which the acute bone destruction of acute osteomyelitis was present, but in all cases there was evidence of healed or healing osteomyelitis. The roentgenograms were investigated from the standpoint of sequestrums, arrangement of trabeculation and density. The amount of sclerosis or increased density

was always directly proportional to the immaturity of the trabeculae. The appearance of normal trabeculae is evidence of the fact that the original involucrum or osteoblastic apposed bone has been reworked into normal bone through the demands of stress and strain. Sequestrums, no matter how small, must be interpreted as evidence of infection, since a sequestrum is either surrounded by pus, in which event it persists indefinitely, or it is surrounded by granulation tissue, in which event it is being slowly absorbed. The rate of absorption is relative to the size of the sequestrum, the blood supply and the density of the surrounding bone. Close examination of roentgenograms of areas of healed osteomyelitis, particularly with a magnifying lens, will often disclose sequestrums that are not observed on a less detailed search. A small sequestrum has the same appearance as a larger one, namely, an area of increased density surrounded by an area of porosis, the whole being surrounded by dense bone. The inner dense body is the sequestrum, and the porotic area represents the pus or granulation. The whole is surrounded by sclerotic bone.

There were 14 cases of healed osteomyelitis in which operation was performed through the site of the previous infection and in which roentgenograms were available for study. These 14 cases fell into three classifications when the sequestrums, trabeculations, density and recurrence of infection were considered.

*Group I* (fig 2) —Four cases, in which there were normal trabeculations, normal density, no sequestrums and no recurrence of infection.

*Group II* (fig 3) —Five cases, in which there were abnormal trabeculations, increased density, no sequestrums, and recurrence of infection in 60 per cent.

*Group III* (fig 4) —Five cases, in which there were abnormal trabeculations, increased density, the presence of sequestrums and recurrence of infection in 100 per cent.

From these groups it is then seen that the presence of sequestrums in the operative field is indicative of recurrent infection. Abnormal trabeculations, the characteristic of the second group, must be considered as a danger sign, since in 60 per cent of this group infection recurred. The normal-appearing bone in the first group represents areas of healed osteomyelitis that can be operated on without recurrence of infection. It then appears that the more nearly the osteomyelitic bone has reconstructed itself to normal, the less chance is there of recurrence of infection.

Roentgenograms in 14 cases of healed traumatic osteomyelitis were also investigated, but it was impossible to form a correlation between the roentgen appearance and the recurrence of infection.



Fig 2—*A*, roentgenogram of a knee that was operated on through the supracondylar area. This is an example of group I in the roentgen classification of healed osteomyelitis. This is the type that does not recur and is characterized by normal trabeculation, no sequestrums and normal density. The enlargement (*B*) shows the characteristics in detail.



Fig 3—*A*, roentgenogram of healed osteomyelitis in a patient operated on in the hip joint area. It is an example of group II in the roentgen classification of healed osteomyelitis. This group is characterized by abnormal trabeculae, no sequestrums and sclerosis with recurrence in 60 per cent of cases. The enlargement of the joint surface (*B*) shows the abnormal trabeculae in detail.



## CONCLUSIONS

1 Gonorrheal arthritis, once it is healed, does not recur after operative trauma. Subsidence of the acute infection and return to the normal afebrile state for six months should be a sufficient interval.

2 Pure suppurative arthritis, when healed, recurs in only 13 per cent of cases when operation is performed through the previously involved area.



Fig. 4—*A*, roentgenogram showing healed osteomyelitis of the tibia and ankle. In this case operation was done in the ankle area. It is an example of group III in the roentgen classification, that is, the group characterized by abnormal trabeculation, sclerosis, sequestrums and recurrence in all cases. The enlargement (*B*) shows the numerous small sequestrums indicative of recurrent infection.

3 Hematogenous osteomyelitis, when operation is performed through the previously involved area, recurs in 46 per cent of cases.

4 Operations carried out near but not through an area of previous osteomyelitis or suppurative arthritis carry a very low frequency of

recurrence of the infection This was 25 per cent for osteomyelitis and 8 per cent for suppurative arthritis in the present study

5 The time for which the infectious process has been quiescent has no relation to the recurrence of infection

6 By careful analysis of the roentgen appearance of healed osteomyelitis it is possible to anticipate which infections will recur in the event of surgical intervention

7 The complication of recurrence is a major affair and should be avoided whenever possible

# RECURRENT INGUINAL HERNIAS

## A STUDY OF TWO HUNDRED AND EIGHTY-TWO HERNIAS AND TWO HUNDRED AND SIXTY-EIGHT REPAIRS

HAROLD J. SHELLEY, M.D.

FORT WORTH, TEXAS

This study covered 282 recurrent inguinal hernias, of which 268 were repaired<sup>1</sup> Included were all hernias of this type in patients admitted to the wards of St. Luke's Hospital, New York, from 1926 to 1935 and all repaired between 1916 and 1925 and followed postoperatively for nine months or longer They comprised 6.4 per cent of all hernias for these two periods and 7.7 per cent of the total inguinal hernias

Of the 268 hernia repairs, 210 were observed postoperatively for nine months or longer (the average follow-up time was thirty-eight and four-tenths months) Among these were found 39 recurrences, giving an incidence of recurrence of 18.6 per cent The average postoperative time after which these recurrences were first noted was nineteen and six-tenths months Only 3 (7.7 per cent) of these recurrences were indirect, and 36 (92.3 per cent) were direct

### ETIOLOGIC FACTORS

*Age at Onset (Age at which Hernia was First Noted)*—This was necessarily determined by the ages of the patients when their hernias were first repaired and the elapsed time between repair and the time at which the recurrences were first noted Consequently, a table giving the various age incidences was not considered to be of any particular value

*Indirect Inguinal Recurrences* The average age of the patients when the indirect recurrences were first noted was 36.7 years, as compared with 30.9 years for patients with primary incomplete indirect inguinal hernias<sup>1a</sup> and 9 years for patients with complete indirect inguinal hernias<sup>1b</sup>

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From the Surgical Services of St. Luke's Hospital

1 All references to types of hernias other than recurrent inguinal hernias are from the following papers published by me (a) Incomplete Indirect Inguinal Hernias A Study of 2,462 Hernias and 2,337 Repairs, Arch Surg 41 747-771 (Sept.) 1940, (b) Complete Indirect Inguinal Hernias A Study of 305 Hernias and Repairs, South Surgeon 9 257-268 (April) 1940, (c) Direct Inguinal Hernias A Study of 605 Hernias and 565 Repairs, Arch Surg 41 857-872 (Oct.) 1940, (d) Femoral Hernias A Study of 238 Hernias and 226 Repairs, ibid. 41 1229-1243 (Nov.) 1940, (e) Ventral Hernias A Study of 550 Hernias and 458 Repairs, South Surgeon 9 617-656 (Sept.) 1940

Direct Inguinal Recurrences The average age at which the direct recurrences were first noted was 42·8 years This age is two years greater than the average age, 40·8 years, at which primary direct inguinal hernias were first noted, but it is less than the average age, 43·7 years, at which the primary repairs were performed<sup>1c</sup> The reasons for this

TABLE 1—*Indirect Inguinal Recurrences Age at Time of Admission or Operation*

Age Group (Years)	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 10	1	0·8	3·9	1	1	100·0	100·0
10 to 20	4	3·1		2	2	100·0	
20 to 30	33	25·8	48·4	26	2	7·7	10·4
30 to 40	29	22·6		22	3	13·6	
40 to 50	29	22·6	42·9	20	2	10·0	7·7
50 to 60	26	20·3		19	1	5·3	
60 to 70	6	4·7	4·7	5	0	0·0	0·0
Totals	128	100·0	100·0	95	11	11·6	11·6

The average age of the patients at time of admission or operation for indirect inguinal recurrences was 39·6 years

TABLE 2—*Direct Inguinal Recurrences Age at Time of Admission or Operation*

Age Group (Years)	Total Hernias	Per Cent of Entire Group		Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	
0 to 10	0	0·0	0·0				
10 to 20	0	0·0					
20 to 30	11	7·1	31·3	9	2	22·2	18·0
30 to 40	38	24·2		30	5	16·7	
40 to 50	55	35·5	53·1	42	12	28·6	27·5
50 to 60	35	22·6		27	7	25·9	
60 to 70	14	9·0	9·7	6	2	33·3	8·6
70 to 80	1	0·7		1	0	0·0	
Totals	154	100·0	100·0	115	23	21·4	21·4

The average age at the time of admission or operation for direct inguinal recurrences was 45·4 years

are 1 A considerable number of direct recurrences followed repairs of indirect hernias and indirect recurrences 2 Not all the recurrences in the older patients were repaired

*Age at Time of Admission or Operation*—Indirect Inguinal Recurrences The average age at the time of operation for these hernias was 39·6 years This compared with 34·8 years for primary incomplete hernias and 16·2 years for complete indirect inguinal hernias The incidences were distributed fairly evenly in the decades from 20 to 40

years, ranging from 25.8 to 20.3 per cent. In all 3 repairs on patients under 20 years of age which were followed for nine months or longer, recurrences developed. This might indicate that not sufficient importance was attributed to this condition in young patients and that consequently inadequate repairs were done. Recurrences developed in 10.4 per cent of patients between the ages of 20 and 40 and in 7.7 per cent between 40 and 60 years. This difference might also be due to the reason just suggested.

**Direct Inguinal Recurrences** The average age at the time of admission or operation for direct recurrences was 45.4 years. This was one and seven-tenths years greater than the corresponding figure for primary

TABLE 3—*Indirect Inguinal Recurrences Sex Incidence*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recurrences	Per Cent Recurrences
Male	115	89.8	84	11	12.4
Female	13	10.2	11	0	0.0
Totals	128	100.0	95	11	11.6

TABLE 4—*Direct Inguinal Recurrences Sex Incidence*

Sex	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recurrences	Per Cent Recurrences
Male	140	94.3	108	28	24.1
Female	9	5.7	7	2	28.6
Totals	149	100.0	115	30	24.4

direct inguinal hernias, 43.7 years, and five and eight-tenths years greater than that for indirect inguinal recurrences, 39.6 years.

No repairs were done on patients under 20 years of age. Thirty-one and three-tenths per cent of the patients were between 20 and 40, 58.1 per cent between 40 and 60 and 9.7 per cent between 60 and 80. The recurrence incidence showed an increase with the patients' ages at the time of operation, as follows: up to 20, no repair; 20 to 40, 18 per cent; 40 to 60, 27.5 per cent, and 60 to 80, 28.6 per cent.

**Sex—Indirect Inguinal Recurrences** The sex incidence among patients with indirect inguinal recurrences, males 89.8 per cent and females 10.2 per cent, was essentially the same as that found in patients entering the hospital during the same period for original repairs of incomplete indirect inguinal hernias, males 88.7 per cent and females 11.3 per cent. The number of females in this group was too small for the absence of recurrences to have any definite significance.

**Direct Inguinal Recurrences** The percentage of males in this group, 94.3 per cent, was slightly less than in the group with primary direct inguinal hernias, 96.9 per cent. The percentage of recurrences was practically the same in male and female patients, 24.1 per cent for males and 28.6 per cent for females, after repair of direct inguinal recurrences, as contrasted to 15.2 per cent for males and 5.5 per cent for females after repair of primary direct inguinal hernias.

**Race**—**Indirect Inguinal Recurrences** As with the race incidence among the admissions for primary repairs of incomplete indirect inguinal hernias, that for indirect inguinal recurrences, white 93.8 per cent and Negro 6.2 per cent, checked with the racial incidence of general admissions to the hospital.

TABLE 5—*Indirect Inguinal Recurrences* Race

Race	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
White	120	93.8	91	11	12.1
Negro	8	6.2	4	0	0.0
Totals	128	100.0	95	11	11.6

TABLE 6—*Direct Inguinal Recurrences* Race

Race	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
White	151	98.1	114	28	24.5
Negro	3	1.9	1	0	0.0
Totals	154	100.0	115	28	24.4

**Direct Inguinal Recurrences** The preponderance of white patients in this group, 98.1 per cent, was greater than that found in the case of either primary direct inguinal hernias, 94.7 per cent, or indirect inguinal recurrences, 93.8 per cent.

The numbers of Negro patients in both groups were too small for the absence of recurrences to have any particular significance.

**Trauma**—**Indirect Inguinal Recurrences** The figures for the incidence of a history of definite trauma as the etiologic factor in the indirect inguinal recurrences (no such history in 73.4 per cent and the presence of such a history in 26.6 per cent) checked exactly with the corresponding figures for the primary incomplete indirect inguinal hernias. As with repair of the latter type of hernias, the incidence of recurrence following repair of indirect inguinal recurrences was definitely less if the history of a traumatic cause was given, 8.3 per cent, as contrasted

an incidence of 12.7 per cent when no such history was given (see footnote to table 7)

**Direct Inguinal Recurrences** The incidence of definite trauma given as the cause of the direct inguinal recurrences was one third less, 20.1 per cent, than that for primary direct hernias, 31.4 per cent. The recurrence rate, 29.6 per cent, in the presence of a definite history of trauma was slightly greater than when such a history was absent, 22.7 per cent.

TABLE 7—*Indirect Inguinal Recurrences History of Definite Trauma as Etiologic Factor\**

History of Trauma as Cause *	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Absent.	91	73.4	71	9	12.7
Positive *	31	26.6	24	2	8.3
Totals	122	100.0	95	11	11.6

\* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma which served only to call the patients attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor was given by 26 per cent of the patients who first noticed their hernias after the age of 15 (Shelley H. J. Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs. South. Surgeon 9: 257-268 [April] 1940).

TABLE 8—*Direct Inguinal Recurrences History of Definite Trauma as Etiologic Factor\**

History of Trauma as Cause *	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Absent.	123	79.9	83	20	22.7
Positive *	31	20.1	27	8	29.6
Totals	154	100.0	110	28	24.4

\* Undoubtedly all or a major part of these hernias were present before the incidence of the trauma, which served only to call the patients attention to the presence of the hernia. In this connection it is interesting to note that among the 305 complete (congenital) indirect inguinal hernias studied, a history of definite trauma as the etiologic factor was given by 26 per cent of the patients who first noted their hernias after the age of 15 (Shelley H. J. Complete Indirect Inguinal Hernias. A Study of 305 Hernias and Repairs, South. Surgeon 9: 257-268 [April] 1940).

This is in contrast to lower recurrence rates when a history of traumatic causation was given with the primary indirect and direct and recurrent indirect inguinal hernias (see footnote to table 8).

#### SYMPTOMS

**Pain**—Indirect Inguinal Recurrences A history of the association of pain with these recurrent hernias was somewhat higher, 60.1 per cent, than that given for the primary incomplete indirect inguinal hernias, 49.7 per cent.

**Direct Inguinal Recurrences** Essentially the same proportion of the direct recurrences were the cause of pain, 49.3 per cent, as was the case with primary direct inguinal hernias, 52.2 per cent.

TABLE 9—*Indirect Inguinal Recurrences History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	51	39.9
Positive	77	60.1
Totals	128	100.0

TABLE 10—*Direct Inguinal Recurrences History of Pain Associated with Hernia*

History of Pain	Total Hernias	Per Cent of Entire Group
Absent	78	50.7
Positive	76	49.3
Totals	154	100.0

TABLE 11—*Indirect Inguinal Recurrences Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recurrences	Per Cent Recurrences
To 1 week	11	8.6	5	0	0.0
To 1 month	25	19.5	15	2	13.3
First 6 months	58	45.3	42	7	16.7
Second 6 months	21	15.7	18	2	11.1
To 1 year	82	64.1	60	9	15.0
0 to 5 years	107	83.6	81	9	11.1
5 to 10 years	12	9.4	7	0	0.0
0 to 10 years	119	92.9	88	9	10.2
10 to 20 years	6	4.7	4	2	50.0
20 to 30 years	2	1.6	2	0	0.0
30 to 40 years	0	0.0			
40 to 50 years	1	0.8	1	0	0.0
Totals	128	100.0	95	11	11.6

The average duration (elapsed period from the time the hernia was first noted to time of operation) of indirect inguinal recurrences was 2.9 years

TABLE 12—*Direct Inguinal Recurrences Duration (Time Hernia Was First Noted to Time of Admission or Operation)*

Duration	Total Hernias	Per Cent of Entire Group	Number Followed Post- operatively	Number of Recurrences	Per Cent Recurrences
To 1 week	8	5.2	7	2	28.6
To 1 month	26	16.9	21	7	33.3
First 6 months	56	36.4	46	13	29.6
Second 6 months	24	15.6	17	0	0.0
To 1 year	80	52.0	63	13	20.6
0 to 5 years	127	82.5	95	23	24.2
5 to 10 years	12	7.8	9	3	33.3
0 to 10 years	139	90.3	104	26	25.0
10 to 20 years	13	8.5	10	2	20.0
20 to 30 years	1	0.7	0		0.0
30 to 40 years	1	0.7	1	0	
Totals	154	100.0	115	28	24.4

The average duration (elapsed period from the time the recurrence was first noted to time of admission or operation) of direct inguinal recurrences was 2.6 years



*Duration*—Indirect Inguinal Recurrences The average elapsed time from the discovery of these recurrences to the time of operation was two and nine-tenths years as compared with three and nine-tenths years for the primary incomplete indirect inguinal hernias

*Direct Inguinal Hernias* The average duration of the direct recurrences was two and six-tenths years as compared with two and nine-tenths years for the primary direct hernias

TABLE 13—*Indirect Inguinal Recurrences* Size

Size of Hernia *	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	30	28.1	22	1	4.5	0 in 31 operations	0.0
Size II	47	30.7	33	8	21.2	0 in 31 operations	0.0
Size III	45	35.2	35	2	5.7	0 in 24 operations	0.0
Totals	123	100.0	95	11	11.6	0 in 86 operations	0.0

\* Size I Hernias in which the sac was limited in extent to the inguinal canal  
 Size II Hernias in which the sac extended beyond the external ring but not into the scrotum  
 Size III Hernias in which the sac extended into the scrotum

TABLE 14—*Direct Inguinal Recurrences* Size

Size of Hernia *	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Size I	57	37.0	44	7	15.7	1 in 37 operations †	2.7
Size II	66	42.9	50	13	26.0	0 in 37 operations	0.0
Size III	31	20.1	21	8	38.1	1 in 13 operations †	7.6
Totals	154	100.0	115	28	24.4	2 in 87 operations †	2.3

\* Size I Hernias in which the sac was limited to the inguinal canal  
 Size II Hernias in which the sac extended beyond the external ring but not into the scrotum  
 Size III Hernias in which the sac extended into the scrotum.  
 † The hernias were not strangulated in either of the 2 patients who died postoperatively

The numbers of followed repairs in the various durations of both types of recurrent hernias were too small to give any definite indications as to any effect the duration might have on the expectancy of recurrence after repair

#### PHYSICAL FINDINGS

*Size*—Indirect Inguinal Recurrences The incidences of the three sizes (see table 13 for definition of the sizes) of these hernias were essentially the same as with the primary hernias. That the majority of the recurrences should have followed repair of hernias which extended beyond the external ring but not into the scrotum is not readily explained. However, in such small groups of followed repairs the recurrence rates are not necessarily accurate

**Direct Inguinal Recurrences** The sac of the direct inguinal recurrent hernia entered the scrotum in a larger proportion of instances, 20.1 per cent, than was found to be the case with the primary direct hernias, 12.4 per cent. Apparently the size of these recurrent hernias influenced the probability of a second recurrence after repair, as follows: sac limited to the inguinal canal, 15.7 per cent of recurrences, sac extending beyond the external ring but not into the scrotum, 26 per cent of recurrences, and scrotal hernias, 38.1 per cent of recurrences. The same was found true with the primary indirect and direct hernias, but without as great a difference.

TABLE 15—*Indirect Inguinal Recurrences Unilateral and Bilateral\**

	(A)				
	Total Hernias	Per Cent of Entire Group	Number Followed Post-operatively	Number of Recurrences	Per Cent Recurrences
Unilateral, right	43	33.6	33	3	9.1
Unilateral, left	19	14.8	11	1	9.1
Total unilateral	62	48.5	44	4	9.1
Total bilateral	63	51.5	51	7	13.9
Total right	77	60.2	60	8	13.3
Total left	51	39.8	35	3	8.3
Totals	125	100.0	95	11	11.6
	(B)				
By original operation					
Two sides repaired separately	recurrences, 9.5%				
Two sides repaired at one operation	recurrences, 13.3%				
By this operation					
Two sides repaired separately	recurrences, 15.6%				
Two sides repaired at one operation	recurrences, 5.3%				
	(C)				
Recurrences	indirect, 10.0%, direct, 90.0%				

\* Each hernia was counted individually. Each indirect inguinal recurrence was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

**Unilateral and Bilateral Hernias**—All the hernias in this study were considered individually. A recurrent hernia was considered as one of two bilateral hernias when another inguinal hernia of any type was present at the same time, had been present previously or appeared later on the opposite side.

**Indirect Inguinal Recurrences** The incidence of bilateral hernias in this group, 51.5 per cent, was definitely greater than that of the original incomplete indirect inguinal hernias, 32.7 per cent. This is readily understood, as the incidence of recurrences was approximately 50 per cent greater after repair of the original bilateral indirect hernias than after repair of the primary unilateral hernias. The same was observed after repair of bilateral indirect recurrences (13.9 per cent recurrences as compared with 9.1 per cent recurrences for the unilateral hernias).

Direct Inguinal Recurrences The incidence of bilateral hernias in this group, 53.2 per cent, was not quite as large as was that found for primary hernias, 59.1 per cent. However, the increased recurrence rate, 27.7 per cent for bilateral hernias and 20 per cent for unilateral hernias, was more definite than that observed after repair of primary bilateral direct hernias, 15.4 per cent, as compared with 14.1 per cent for primary unilateral repairs.

TABLE 16—*Direct Inguinal Recurrences Unilateral and Bilateral\**

	Total Hernias	Per Cent of Entire Group	Number Followed Post operatively	Number of Recurrences	Per Cent Recurrences
Unilateral right	41	26.6	28	6	21.4
Unilateral, left	31	20.1	22	4	18.2
Total unilateral	72	46.8	50	10	20.0
Total bilateral	82	53.2	65	18	27.7
Total right	82	53.2	61	15	24.6
Total left	72	46.8	54	13	24.1
Totals	154	100.0	115	28	24.4

\* Each hernia was counted individually. Each direct inguinal recurrence was considered one of two bilateral inguinal hernias when there was or had been an inguinal hernia of any type on the opposite side.

TABLE 17—*Indirect Inguinal Recurrences Incarceration and Strangulation*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	116	90.7	87	0	10.3	0 in 78 operations	0.0
Incarcerated *	10	7.8	6	2	33.3	0 in 6 operations	0.0
Strangulated *	3	2.3	3	0	0.0	0 in 2 operations	0.0
Totals	128	100.0	95	11	11.6	0 in 86 operations	0.0

\* Strangulation developed in 1 old incarcerated hernia.

TABLE 18—*Direct Inguinal Recurrences Incarceration and Strangulation*

Incarcerated or Strangulated	Total Hernias	Per Cent of Entire Group	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Operative Deaths (1926-1935)	Per Cent Mortality
Neither	140	91.1	105	24	23.8	2 in 78 operations	2.6
Incarcerated	8	5.1	6	1	16.7	0 in 8 operations	0.0
Strangulated *	6	3.8	4	3	75.0	0 in 3 operations	0.0
Totals	154	100.0	115	28	24.4	2 in 87 operations	2.3

\* Two patients who had strangulated hernias were not operated on, as they were moribund when admitted to the hospital. Both died.

*Incarceration and Strangulation*—Indirect Inguinal Recurrences The incidences of incarceration and strangulation were slightly greater for the recurrences, 7.8 and 2.3 per cent respectively, than for the primary hernias, 6 and 1.8 per cent respectively.

Direct Inguinal Recurrences This increase was even more marked with the direct recurrences, 5.1 and 3.8 per cent, as compared with 3.1 and 1.6 per cent for primary direct inguinal hernias.

The numbers of hernias studied in the various groups of both types of recurrent hernias were too small for the respective recurrence rates to have any definite significance

### RESULTS ACCORDING TO TYPE OF REPAIR

Because of the relatively small numbers of followed cases with each of the various types of repairs, the recurrence rates are undoubtedly inaccurate. However, they are given in tables 19 and 20 for whatever they may be worth

TABLE 19—*Indirect Inguinal Recurrences Type of Repair*

Type of Repair *	Total Followed	Per Cent Recur- rences	Per Cent Infections †	Per Cent Infections Showing Recur- rences †	Per Cent Recurrences	
					Indirect	Direct
1	4	25.0	0.0		0.0	100.0
2	36	11.1	2.8	0.0	25.0	75.0
2A	10	10.0	0.0		0.0	100.0
2B	14	7.1	42.8	0.0	0.0	100.0
3	3	33.3	0.0		0.0	100.0
4	8	37.5	12.5	0.0	0.0	100.0
4A	6	0.0	0.0		0.0	100.0
4B	4	0.0	0.0			
5	9	0.0	0.0			
6	1	0.0	0.0			
All repairs without fascial sutures	61	14.8	4.9	0.0	11.1	88.9
All repairs with fascial sutures	34	5.9	17.6	0.0	0.0	100.0
Totals	95	11.6	6.7	0.0	9.1	90.9

\* Type 1 Repairs without transplantation of the cord

Type 2 Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.

Type 2A Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle

Type 2B Same as type 2, with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the fascia lata

Type 3 Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle

Type 4 Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle, with or without overlapping of the aponeurosis

Type 4A Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture from the aponeurosis of the external oblique muscle

Type 4B Same as type 4, with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata

Type 5 Repairs in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament.

Type 6 Repairs in which the testicle and cord were brought down through the femoral opening and into the scrotum

† The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds which were examined in the follow up clinic for nine months or longer

With both types of hernias the two groups, "without fascial sutures" and "with fascial sutures," are large enough for comparative recurrence figures to be obtained. With both types of recurrent hernias the results were favorable to the use of fascial sutures in the repair of these hernias. This difference is particularly outstanding when one considers that in the majority of instances catgut alone was used in the less difficult repairs and fascial sutures in those presenting the greater obstacles to the performance of a satisfactory repair.

TABLE 20—*Direct Inguinal Recurrences Type of Repair*

Type of Repair *	(A)					
	Total Followed	Per Cent Recurrences	Per Cent Infections †	Per Cent Infections Showing Recurrences †	Per Cent Recurrences	
					Indirect	Direct
1	4	0 0	0 0			
2	23	34 7	0 0			
2A	6	16 7	16 7	0 0	0 0	100 0
2B	20	11 5	3 3	100 0	0 0	100 0
3	3	66 7	0 0		0 0	100 0
4	16	37 5	6 3	0 0	16 7	83 3
4A	5	20 0	20 0	0 0	0 0	100 0
4B	7	14 3	0 0		0 0	100 0
5	25	24 0	4 0	0 0	16 7	83 3
Totals	115	24 4	3 6	14 3	7 1	92 9
(B)						
All repairs without fascial sutures	71	31 0	2 8	0 0		
All repairs with fascial sutures	44	13 6	6 8	20 0		
Totals	115	24 4	3 6	14 3		

\* Type 1 Repairs without transplantation of the cord  
 Type 2 Repairs with transplantation of the cord between the conjoined tendon and the aponeurosis of the external oblique muscle.  
 Type 2A Same as type 2 with suture of the conjoined tendon and the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle  
 Type 2B Same as type 2 with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata  
 Type 3 Repairs with transplantation of the cord between the overlapped layers of the aponeurosis of the external oblique muscle  
 Type 4 Repairs with transplantation of the cord external to the aponeurosis of the external oblique muscle with or without overlapping of the aponeurosis  
 Type 4A Same as type 4 with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the aponeurosis of the external oblique muscle  
 Type 4B Same as type 4 with suture of the conjoined tendon to the inguinal ligament with a fascial suture obtained from the fascia lata  
 Type 5 Repairs in which the rectus muscle or the anterior rectus sheath was sutured to the inguinal ligament  
 † The percentages of infections were calculated on the entire number of repairs in each group. The percentages of infected wounds showing recurrences were calculated according to the number of recurrences found among the total infected wounds in each group which were examined in the follow up clinic for nine months or longer

TABLE 21—*Indirect Inguinal Recurrences Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	13	10 2	17 8	11	1	9 1	0 0	0	0 0
2 Wound Infection	9	7 0	19 0	6	0	0 0		0	0 0
3 Hematomas	3	2 3	20 0	2	0	0 0	0 0	0	0 0
4 Pulmonary embolus	2	1 6	46 0	2	0	0 0	0 0	0	0 0
5 Acute otitis media	1	0 8	13 0	1	0	0 0	0 0	0	0 0
6 Empyema	1	0 8	55 0	1	0	0 0	0 0	0	0 0
7 Central pneumonia	1	0 8	18 0	1	0	0 0	0 0	0	0 0
8 Prostatic abscess	1	0 8	25 0	0			0 0	0	0 0
9 Hiccups	1	0 8	19 0	1	0	0 0	0 0	0	0
Totals	32	25 0		25	1	4 0	0 0*	0	0 0

\* Excluding those patients whose only complication was wound infection

TABLE 22—*Direct Inguinal Recurrences Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	8	5.7	17.1	7	3	42.9	12.5	0	0.0
2 Wound infection	5	3.0	20.2	3	1	33.3		0	0.0
3 Broncho pneumonia	4	2.9	18.5	3	1	33.3	0.0	1	25.0
4 Hematomas	3	2.1	17.3	3	0	0.0	0.0	0	0.0
5 Lobar pneumonia	1	0.7	18.0	1	0	0.0	0.0	0	0.0
6 Coronary occlusion	1	0.7	0.0				0.0	1	100.0
7 Pyelitis	1	0.7	20.0	0	—	—	0.0	0	0.0
Totals	23	10.1	—	17	5	29.5	5.8*	2	8.7

\* Excluding those patients whose only complication was wound infection.

TABLE 23—*Indirect Inguinal Recurrences Respiratory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	13	10.2	17.8	11	1	9.1	0.0	0	0.0
2 Pulmonary embolus	2	1.0	46.0	2	0	0.0	0.0	0	0.0
3 Acute otitis media	1	0.8	13.0	1	0	0.0	0.0	0	0.0
4 Empyema	1	0.8	55.0	1	0	0.0	0.0	0	0.0
5 Central pneumonia	1	0.8	18.0	1	0	0.0	0.0	0	0.0
Totals	18	14.1	—	16	1	6.3	0.0	0	0.0

TABLE 24—*Direct Inguinal Recurrences Respiratory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post-Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1 Acute bronchitis	8	5.7	17.4	7	3	42.9	12.5	0	0.0
2 Broncho pneumonia	4	2.9	18.5	3	1	33.3	0.0	1	25.0
3 Lobar pneumonia	1	0.7	18.0	1	0	0.0	0.0	0	0.0
Totals	13	9.3	—	11	4	38.4	7.7	1	7.7

Recurrences followed 14.8 per cent of the repairs of indirect inguinal recurrent hernias done with catgut alone and only 5.9 per cent when a fascial suture was used. However, four times as many wound infections developed after the use of the latter, 17.6 per cent, than when catgut suture material alone was employed, 4.9 per cent. However, none of the infections in either instance was followed by recurrence of the hernia.

In the case of repairs of direct inguinal recurrences, a second recurrence appeared after the use of catgut alone in 31 per cent, and this happened in only 13.6 per cent when fascial sutures were used. This

TABLE 25—*Indirect Inguinal Recurrences Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas	3	2.3	20.0	2	0	0.0	0.0	0	0.0
2. Pulmonary embolus	2	1.6	46.0	2	0	0.0	0.0	0	0.0
Totals	5	3.9	—	4	0	0.0	0.0	0	0.0

TABLE 26—*Direct Inguinal Recurrences Circulatory Postoperative Complications*

Complication	Total Operations	Per Cent of Entire Group	Average Post Operative Stay in Hospital, Days	Number Followed Postoperatively	Number of Recurrences	Per Cent Recurrences	Per Cent Infected Wounds	Deaths	Per Cent Mortality
1. Hematomas	3	2.1	17.3	3	0	0.0	0.0	0	0.0
2. Coronary occlusion	1	0.7	6.0	—	—	—	0.0	1	100.0
Totals	4	2.8	—	3	0	0.0	0.0	1	25.0

held true even though the incidence of infected wounds was increased from 2.8 per cent to 6.8 per cent, and 20 per cent of the patients with infected wounds in which fascial sutures were employed had a recurrence later.

#### POSTOPERATIVE COMPLICATIONS

*Indirect Inguinal Recurrences*—Postoperative complications followed 25 per cent of the repairs of indirect inguinal recurrences. This was two and one-half times as great an incidence as followed the primary repairs of incomplete indirect inguinal hernias. However, none of these complications caused the death of a patient. Acute bronchitis was the only complication followed by a recurrence, and for the group of repairs fol-

lowed by some postoperative complication the recurrence rate was only 9.1 per cent, as compared with 11.6 per cent for all repairs of indirect inguinal recurrences

Respiratory complications followed 14.1 per cent, as compared with 7.3 per cent of the primary repairs. The increase in the incidence of circulatory complications was less marked, 3.9 per cent as compared with 2.8 per cent. Wound infection developed in 7 per cent, as compared with 3.5 per cent in the repairs of the primary incomplete indirect inguinal hernias

*Direct Inguinal Recurrences*—The increased incidence of postoperative complications found in the group of hernias just under discussion was not observed in repairs of direct inguinal recurrences. The figures were repairs of recurrences, 16.4 per cent, and primary repairs, 21.1 per cent. Bronchopneumonia and coronary occlusion were each the cause of 1 death

TABLE 27—*Direct Inguinal Recurrences Deaths (1926-1935)*

Operative Deaths *	Patient's Age	Hernia Strangulated	Duration of Strangulation	Resection Required	Time of Death (Post operative)	Cause of Death
1	48	No			20 days	Bronchopneumonia
2	50	No			6 days	Coronary occlusion

\* Two deaths in 87 operations, giving an operative mortality of 2.3 per cent

Two patients died who were not operated on. They were moribund when admitted with strangulated hernias, one of 8 days' duration and the other of 3 weeks' duration. One patient was 60 and the other 63 years of age

Respiratory complications followed 9.3 per cent of repairs of the direct recurrences, as compared with 13.3 per cent of the primary repairs, and the figures for circulatory complications were 2.8 and 3 per cent respectively

The main complications in the two groups of repairs appeared in the same sequence

#### OPERATIVE MORTALITY

No deaths followed the 86 repairs of indirect inguinal recurrences performed in the ten year period from 1926 to 1935 inclusive

Two deaths followed the 87 repairs of direct inguinal recurrences done in the ten year period 1926 to 1935. One patient, 50 years of age, died on the sixth postoperative day owing to a coronary occlusion. The other was 48 years of age and died of bronchopneumonia on the twentieth postoperative day. Neither of the two hernias had been strangulated

One patient, aged 60 years, entered the hospital moribund, with a strangulation of three weeks' standing. She died immediately after admission, no attempt having been made to repair the hernia. The same was true of another patient, 68 years of age, with a strangulation present eight days before admission to the hospital



## FOLLOW-UP DATA

*Indirect Inguinal Recurrences*—In this group 128 hernias were studied, all of which were repaired. Twenty-two patients did not return for follow-up examination. Eleven were observed postoperatively for less than nine months without a recurrence having been discovered. Ninety-five patients were followed for nine months or longer or were found to have a recurrence within less than nine months.

TABLE 28—*Indirect Inguinal Recurrences Follow-Up Data*

Total number of hernias studied	128
Total with no operation	0
Total operations	128
Total operative deaths	0
Total with no follow up examination	22
Total with follow up under 9 months (no recurrence)	11
Total with follow up 9 months and over (including recurrences)	95
Average follow up time (all cases followed 9 months and over)	36 months
Total recurrences	11
Average postoperative time recurrences were first noted	18.5 months
Percentage of recurrences (follow up 9 months and over)	11.6
Total number of operations examined postoperatively	103
Average follow up time (all followed cases)	32.1 months
Total recurrences	11
Percentage of recurrences (all followed cases)	10.5

Recurrences indirect 9.1%, direct 90.9%

TABLE 29—*Direct Inguinal Recurrences Follow-Up Data*

Total number of hernias studied	154
Total with no operation	14
Total nonoperative deaths	2
Total operations	140
Total operative deaths	2
Total with no follow up examination	15
Total with follow up under 9 months (no recurrences)	10
Total with follow up 9 months and over (including recurrences)	115
Average follow up time (all cases followed 9 months and over)	40.4 months
Total recurrences	23
Average postoperative time recurrences were first noted	20.6 months
Percentage of recurrences (follow up 9 months and over)	24.4
Total number of operations examined postoperatively	125
Average follow up time (all followed cases)	37.5 months
Total recurrences	23
Percentage of recurrences (all followed cases)	22.4

Recurrences indirect 7.1%, direct 92.9%

The average length of time over which all followed cases were observed was thirty-two and one-tenth months. The 11 discovered recurrences gave a recurrence rate of 10.5 per cent. The average follow-up period for those followed nine months or more was thirty-six months. Of this group of 95 repairs, recurrences developed in 11, or 11.6 per cent. The average time postoperatively at which the recurrences were first noted was eighteen and one-half months.

Of the 11 recurrences, 90.9 per cent were direct and 9.1 per cent indirect, as compared with 60 per cent direct and 40 per cent indirect after primary repairs of incomplete indirect inguinal hernias

*Direct Inguinal Recurrences*—Of the 154 direct inguinal recurrences studied, 14 were not repaired. Among the 140 patients on whom repairs were performed, 2 died postoperatively, and 15 did not return for follow-up examination. Ten repairs were observed for less than nine months without a recurrence having been discovered. A total of 115 repairs were followed postoperatively for nine months or longer or until a recurrence was noted.

TABLE 30—*Indirect Inguinal Recurrences Sequence of Recurrences When Known*

Type of Original Hernia	Type of Original Operation	Type of Repaired Recurrence	Type of Repair	Type of Present Recurrence	Interval Before Recurrence
Direct		Indirect	Halsted	Direct	2 weeks
Direct		Indirect	Halsted	Direct	6 months
		Indirect	Bassini	Direct	6 months
		Indirect	Galle		
Indirect *		Indirect	Halsted	Direct	8 months
		Indirect	Willys	Direct	12 months
Indirect *			Andrews		
Indirect *		Indirect	Bassini	Direct	13 months
Indirect *	Bassini	Indirect	Ferguson	Direct	13 months
Complete indirect	Ferguson	Indirect	Bassini	Direct	16 months
		Indirect	Bassini	Direct	18 months
Indirect *		Indirect	Bassini	Direct	2½ years
Indirect *	Bassini	Indirect	McArthur		
			Bassini	Indirect	8½ years

\* Hernias listed as indirect without qualification were all incomplete indirect hernias

The average time covered by the follow-up for the 125 repairs observed postoperatively was thirty-seven and one-half months, and the recurrence rate was 22.4 per cent. For the 115 repairs observed for nine months or longer or until a recurrence was noted, the average follow-up time was forty and four-tenths months, and the recurrence rate was 24.4 per cent. The 28 recurrences were discovered after an average postoperative interval of twenty and six-tenths months.

The proportion of direct and indirect recurrences which followed the repair of direct inguinal recurrences was essentially the same as for the primary repairs: 92.9 per cent direct and 7.1 per cent indirect for the former and 90.9 per cent direct and 9.1 per cent indirect for the latter.

#### SEQUENCE OF RECURRENCES

The sequences of the types of operations and recurrences, when known, are presented in tables 30 and 31. The data in these tables are of considerable interest, but the number of cases in which the information was complete was too small to be of value in drawing conclusions.



inguinal ligament, appears to be the logical first step in these repairs. This maneuver prevents the insinuation of pieces of peritoneal fat between the later approximated edges of the conjoined tendon and inguinal ligament.

If the groups of followed cases in this study can be considered sufficiently large for the resultant recurrence rates to be accurate, the conclusion must be drawn that these recurrent inguinal hernias should be repaired by the use of a fascial suture. Several authors have in the past few years advocated the substitution of silk suture technic for the use of fascial sutures. To date at St. Luke's Hospital there are no records of sufficiently large groups of repairs with adequately long follow-up periods to enable one to draw any conclusions in this matter. However, until greater numbers of followed cases in whose repairs silk sutures were used exclusively without selection of cases are available for study, I am of the opinion that the majority of the recurrent inguinal hernias should be repaired with either the McArthur or the Gallie technic, silk being used throughout for sutures, ligatures and fixation of the fascial sutures.

Points as to the general technic of dissection and repair of these hernias are the same as in the repair of the primary inguinal hernias. Among these are careful, clean dissection, maintenance of hemostasis and asepsis, care that sutures are not tied too tightly, inclusion of bleeding vessels only without adjacent tissues in the ligatures and reduction of the size of the cord when necessary at its point of exit through the internal ring.

1213 Medical Arts Building

# CHANGES IN BONES AND JOINTS RESULTING FROM INTERRUPTION OF CIRCULATION

## II NONTRAUMATIC LESIONS IN ADULTS WITH BONE INFARCTION, ARTHRITIS DEFORMANS

DALLAS B PHEMISTER M D  
CHICAGO

The recognized causes of interruption of the circulation and infarction of the viscera are embolism, thrombosis, arteriosclerosis and obliterative endarteritis. In case of gangrene of the extremities neurogenic vascular spasm (Raynaud's disease) and ergot intoxication must be added to this list. In view of the relative frequency of these circulatory disturbances in adults, it is surprising that similar lesions of bones have not been more frequently reported to accompany them. As was brought out under general considerations in part I of this study, most of the lesions resulting from nontraumatic interruption of circulation of bone in adults that have heretofore been described have not definitely been traced to the aforementioned causes and with some of the lesions to be described here there is much uncertainty either as to the cause or as to the exact mechanism of action of the exciting factor. That arteriosclerosis, obliterative endarteritis and neurogenic and toxic vascular changes may be potential or contributory factors by creating so-called functional end arteries in regions of bone where true end arteries are not normally found is to be borne in mind in attempting an explanation of bone infarction in adults.

### CAISSON DISEASE

It has long been known that caisson disease is due to damage of the tissues by nitrogen, which, having been absorbed in excess by the body under compression, forms bubbles in the tissues and body fluids from too rapid decompression. The nitrogen within the blood vessels produces embolism of the viscera with varying effects, sometimes causing death. Fat and lipoids absorb much greater quantities of nitrogen than do other tissues and body fluids, accounting for the frequent damage and mottling of the subcutaneous tissues. Nitrogen frequently accumulates in bubbles within the spinal cord, where it is liberated from the high lipid content of cord tissue and results in varying degrees of paralysis, especially in

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From the Department of Surgery, the University of Chicago

the lower extremities Bassoe<sup>1</sup> and Bornstein<sup>2</sup> were the first to report a deforming type of arthritis in the hips and shoulders as a sequel of caisson disease, and Bassoe described blotchy roentgen shadows of increased density within the shaft of the tibia in 2 cases. Numerous cases in which articular changes occurred have since been reported, as will be seen by consulting the bibliographies of three of the articles cited<sup>3</sup>

Kahlstrom, Burton and I<sup>3a</sup> reported 4 cases of caisson disease of long standing in which there were bone infarcts, some in the shafts and some in the epiphyses of the long bones, which because of either calcification of their walls or collapse or sequestration from weight bearing were recognizable in roentgenograms. In 3 of the cases there were the changes associated with deforming arthritis, some of which were in the hips and some in the shoulders. The diagnosis was confirmed by necropsy in 1 case and by biopsy in another. Since then the diagnosis in case 4 of the series has been confirmed by a surgical excision, which will be discussed later. The massive bone necrosis was attributed to the liberated nitrogen, but uncertainty was expressed as to the exact method of action. In favor of infarction from nitrogen embolism were the extensive involvement of the diaphysis or of the epiphysis with freedom from involvement of the other and predilection for the head of the femur, which is known to be the most frequent seat of end arteries in the adult skeleton. But against nitrogen embolism is the fact that the infarcts were very extensive and that the extensive embolism of viscera which might be expected to accompany such an amount of bone embolism would be likely to cause death. Since the involved bones were limited to the extremities, since the bones of the extremities are rich in fatty marrow and since fat absorbs relatively a very large amount of nitrogen, a plausible theory is that nitrogen bubbles liberated within the medullary canals, where absorption is slow, kill the tissues by direct compression. When the epiphysis is involved and the necrotic bone borders on the joint, the overlying articular cartilage undergoes either extensive or complete necrosis. Use of the limbs in the presence of the necrosis may cause the head of the femur or of the

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1 Bassoe, P. Compressed Air Disease, *J. Nerv. & Ment. Dis.* **38** 368, 1911, The Late Manifestations of Compressed Air Disease, *Am. J. M. Sc.* **145** 526, 1913

2 Bornstein, A. Versuche ueber die Prophylaxe der Pressluftkrankheit, *Berl. klin. Wchnschr.* **47** 1272, 1910

3 (a) Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. Aseptic Necrosis of Bone. I. Infarction of Bones in Caisson Disease Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, *Surg., Gynec. & Obst.* **68** 129, 1939, II. Infarction of Bones of Undetermined Etiology Resulting in Encapsulated and Calcified Areas in Diaphyses and in Arthritis Deformans, *ibid.* **68** 631, 1939. (b) Coley, B. L., and Moore, M., Jr. Caisson Disease with Special Reference to the Bones and Joints. Report of Two Cases, *Ann. Surg.* **111** 1065, 1940. (c) Ugolotti, F. La forma osteoarticolare della malattia dei cassoni e sua interpretazione medico-legale, *Assistenze sociali* **14** viii, 1940

humerus to collapse, which may greatly deform the joint. Chronic deforming arthritis is a relatively late sequel, its development being secondary to the necrosis of the articular cartilage as first described in association with other conditions by Axhausen<sup>4</sup>. Coley and Moore<sup>3b</sup> have since reported 2 cases of caisson disease with pain and stiffness of long standing in the shoulder and hip joints in which roentgenograms demon-



Fig 1 (case 1) —Caisson disease of three years' duration, producing necrosis in the head of the femur and collapse of the weight-bearing articular surface (x)

strated not only chronic deforming arthritis but large to small circumscribed areas of increased density in the shafts and epiphyses, indicative of bone infarcts. Ugolotti<sup>3c</sup> has recently reported a case of caisson disease in which at the end of twenty months mottled areas of increased

<sup>4</sup> Axhausen G. Arthritis deformans und ihre Abarten. Arch f klin Chir 126 573 1923

and decreased density in the head, neck and trochanteric regions of the femurs and of the head and surgical neck of the left humerus, interpreted as infarcts, were visible in roentgenograms

In the following case of caisson disease there was necrosis of the head of the femur with collapse of the weight-bearing portion, but roentgen signs of chronic arthritis were not yet visible

CASE 1—A C, a man aged 51 years, was seen April 22, 1940. Three years previously the patient, who worked at tunnel construction under 35 pounds (159 Kg) of compressed air, noticed severe pains in the lower limbs about two hours after leaving the compression chamber. Return to the decompression lock did not give relief. The pains continued, and he was confined to bed for three weeks. He then returned to light work but has since continued to have pains in the hips, much more marked in the right than in the left, with extension down the right leg. The right hip is at present lame and weak.

Physical examination revealed him to be large and muscular. He had a slight limp referable to the right hip. There were moderate limitation of rotation and abduction of the right hip joint, but flexion was only slightly limited. Physical examination otherwise showed him to be essentially normal. A roentgenogram (fig 1) of the right hip showed a break in the shadow of the articular cortex underlying the superior acetabular margin (1), with a moderate depression of the weight-bearing portion of the head, extending mesially to the region of the acetabulum. There were mottling and streaking of the shadow of the underlying head and an irregular zone of increased density in the adjacent border of the neck and laterally in the noncollapsed portion of the head. The diagnosis of necrosis of the head followed by collapse of the weight-bearing portion was based on the similarity of the roentgenograms to those in proved cases of necrosis and collapse of the head produced by caisson disease, fracture of the neck of the femur and dislocation of the hip. The changes of chronic deforming arthritis had not yet begun. Roentgenograms of the rest of the body showed a normal bone and joint picture.

Pathologic studies of one shoulder and both hip joints obtained at autopsy in case 1 of the series reported by Kahlstrom, Burton and me (the condition was of thirty-five years' standing) revealed the final stages of such articular changes. There were flattening of the heads of the bones, replacement of articular cartilage by irregularly thinned fibrocartilage, marked lipping of the articular margins, osteocartilaginous loose bodies in the joints, medium to slight chronic villous synovitis, subcortical bony cavities in the heads filled with fibrous tissue or fluid and irregularly arranged living bone which had replaced the old dead bone of the heads.

Resection of the head of the right femur in case 4 of the same series has since given opportunity for pathologic study of the disease in a less advanced stage than that aforementioned. At the time of the original report the disease was of twenty-one years' standing. There was roentgen evidence of flattening and mottled increase in density in the heads of the femurs and humeri, of marginal lipping of their joints and of



faintly walled-off and calcified infarcts in the shafts of the femurs and the tibiae. One year later the patient (case 2 of this series, not reported in detail here) was having great difficulty with the hips in walking. Roentgenograms revealed little or no advance in the lesions of the bones and joints. In figure 2 (the right hip) evidence of marked hiping, irregularity of the weight-bearing portion of articular surface of the head and blotchiness of underlying bone were observed. The major por-

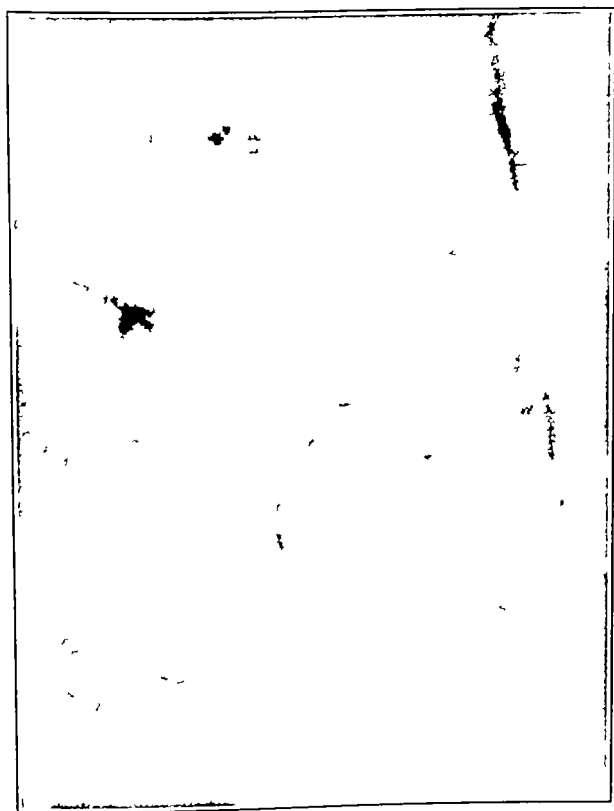


Fig 2 (case 2) —Caisson disease of the right hip of twenty-two years' duration

tion of the head was then resected in an attempt to improve the function of the hip. Marginal osteophytes and moderate villous arthritis were present. Figure 3 is a photograph of a coronal section of the more or less fragmented resected portion. The articular surface of the weight-bearing portion was flattened, and its cartilage was thin and irregular. At one point (1), there was a dense sequestered pea-sized piece of cortical bone and articular cartilage. Figure 4 shows a microscopic section of the head. The bone of the interior was irregularly arranged as if reconstructed and viable. The lateral nonweight-bearing portion of



Fig 3 (case 2) —The two halves of a coronal section of the resected head showing a deformed articular surface and a sequestrum (x) bordering on the joint.



Fig 4 (case 2) —Microscopic section of the head, showing the lateral non weight-bearing surface (x) not collapsed and the weight-bearing surface at the top and mesially (y) irregular and collapsed



Fig 5 (case 2) —Section of a sequestrum (x, fig 3) from the articular surface. The cartilage and bone are dead

the head was covered by a thick layer of fibrocartilage (1) The top of the head had been destroyed, leaving a broad groove partly filled by fibrous tissue which surrounded some dead bony trabeculae Mesial to this there was a thin irregular covering of fibrocartilage The loose



Fig 6—High power view of the section shown in figure 5 Note the dead cartilage and bone, with calcareous deposits in the spaces

piece of cortex (1) of figure 3 was sectioned It was found to consist of old dead articular cartilage and underlying bone similar to a loose body in a case of osteochondritis dissecans (fig 5) On microscopic examination (fig 6) the bony lacunae were seen to be empty, the marrow spaces were partly filled with calcareous deposits and the cartilage was partly detached from the bone This was a portion of the

necrotic head which in the region of greatest weight bearing became detached, remained separate and consequently did not undergo creeping replacement by new bone and fibrocartilage as was the case in the rest of the head

When the necrotic area is located in a diaphysis or in an epiphysis away from the articular cortex, it is invaded by blood vessels and osteo-

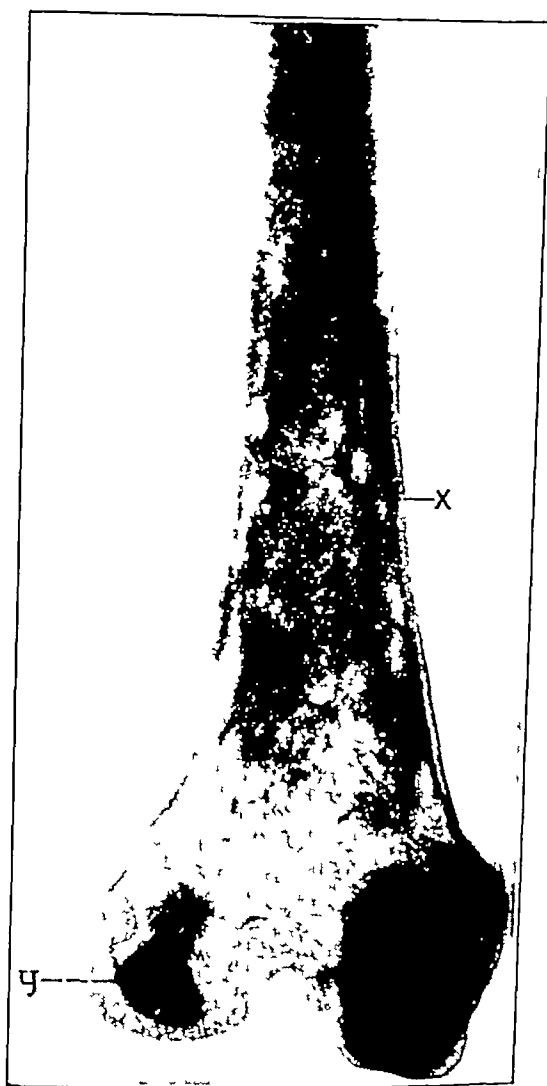


Fig 7—Caisson disease of thirty-five years' duration. Note the old infarcts with a calcified zone of demarcation in the shaft (x) and in the epiphysis (y)

genic elements at its periphery and is gradually reduced in size through creeping substitution by new bone. Smaller infarcts may be in the course of months or years completely replaced by new bone, but in the case of large ones, especially of the shafts, the replacement process comes to a standstill and the remaining necrotic bone becomes walled off by fibrous tissue, which eventually calcifies and ossifies, giving a sharp line of demarcation. The interior may also become calcified in

part, so that after a long time the infarct casts a characteristically dense circumscribed shadow in roentgenograms. Figure 7 is a roentgenogram of the lower half of the necropsy specimen of the right femur in case 1 in the series reported by Kahlstrom, Burton and me. It shows a massive dense infarct in the shaft and a small one in the lateral condyle thirty-five years after the attack of caisson disease. It should be emphasized that roentgenograms taken in the early stages and even after the lapse of a few years may show no shadow outlining the infarct because calcification has not yet set in. A biopsy in case 2 of the aforementioned series, in which the disease was of four years' duration, showed no calcification of the dead bone in the head of the femur. Dr C Howard Hatcher, of this department, has produced caisson disease experimentally in dogs, but in no instance was bone infarction found.

#### ARTERIOSCLEROSIS AND BONE INFARCTION

In the following case of old calcified infarct of the tibia there was marked generalized arteriosclerosis which led to a fatal termination. While there was no direct proof that arteriosclerosis was the cause of the infarction, it appeared to be the most plausible explanation.

CASE 3—A white man aged 52 years consulted Dr C C Burton, who has supplied the following history and permitted study of the involved bone. Four months before coming under Dr Burton's care (Feb 14, 1938), the patient fell and fractured the medial condyle of the right femur. Weight extension was applied to a Steinmann pin through the os calcis, but extensive osteomyelitis developed and was still active on admission.

The past history revealed a normal childhood and adolescence. The patient began work as a coal miner and continued in that occupation for twenty-two years. Then he served in the army during the World War, as an automobile factory worker for eight years and as a janitor up to the date of injury. He never worked in compressed air and never had symptoms of bends or pains in the extremities or in any of the joints.

Physical examination showed him to be well developed. The blood pressure was 100 systolic and 60 diastolic. The Wassermann and Kahn reactions were negative. The urine was within physiologic limits. Regional examination revealed no abnormality except in the right lower extremity. The right knee showed increased lateral mobility. The right ankle was markedly stiff, swollen, tender and tense. There was a sinus discharging pus beneath the external malleolus.

Roentgenograms of the foot and ankle revealed osteomyelitis with marked destruction of the os calcis and osteoporosis of the other bones of the foot and ankle. Roentgenograms of the femur showed a healed fracture of the medial condyle. Roentgenograms of the upper end of the right tibia revealed an area of blotchy increased density situated centrally in the upper  $2\frac{1}{2}$  inches (7.2 cm.) of the diaphysis, measuring approximately 1 inch (2.5 cm.) in diameter above and tapering slightly downward to the lower end. A bone infarct was diagnosed and roentgenograms were then made of the rest of the bones of the extremities but no abnormalities were revealed.

The right leg was amputated 6 inches (15 cm) below the knee because of the osteomyelitis. The patient later wore an artificial limb but did not return to work.

He died suddenly one year and ten months after the operation. The peripheral arteries were noticeably sclerotic. The pleural and peritoneal spaces were clear and free from fluid. There were old healed fractures of the right seventh and eighth ribs. The heart weighed 300 Gm. There were marked arteriosclerosis, calcification and narrowing of the coronary arteries. No gross infarction of the myocardium or valvular disease was observed.

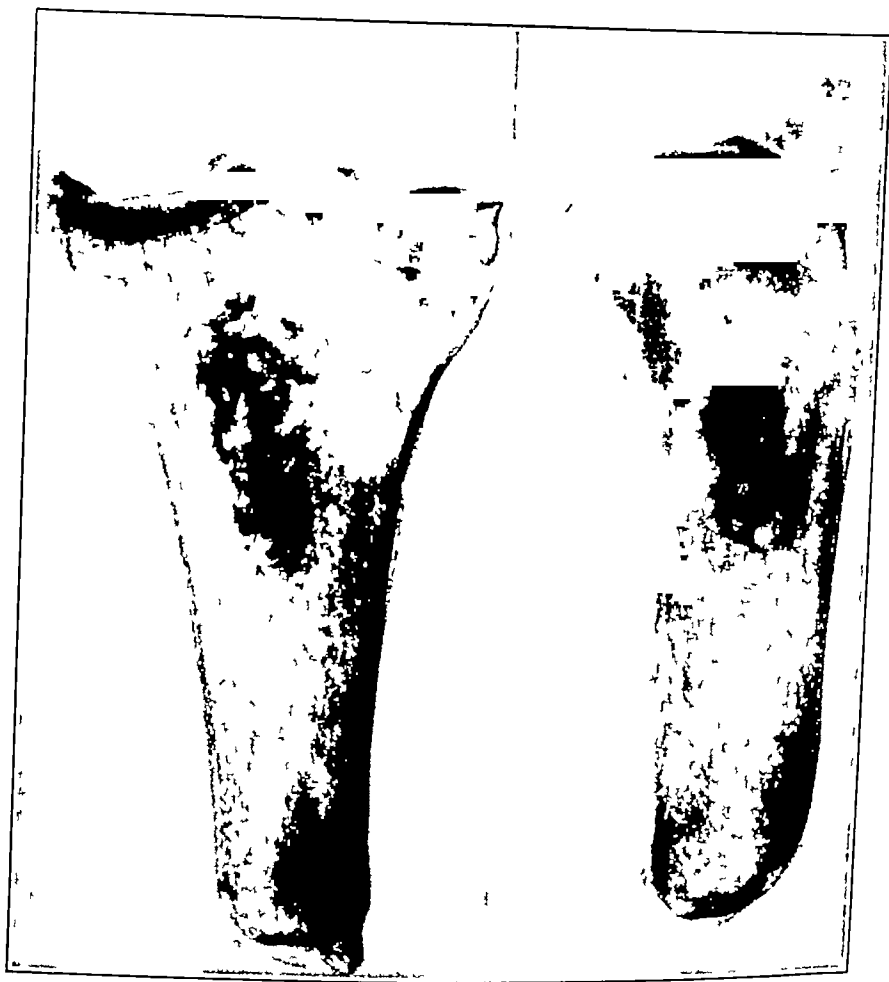


Fig 8 (case 3) —Roentgenograms of the stump of the tibia obtained at autopsy, showing an old infarct of the diaphysis

The entire aorta was atheromatous, with discolored subintimal areas, probably due to hemorrhage. The lungs, liver, spleen and kidneys showed pronounced passive congestion but no evidence of infarcts, recent or old. There were petechial hemorrhages in the spleen and in the pancreas.

Microscopic examination revealed marked generalized arteriosclerosis, coronary arteriosclerosis, degeneration and fatty infiltration of the myocardium and passive congestion of all of the viscera, but no signs of infarcts. The immediate cause of death was heart failure.

The stump of the right tibia was sent for pathologic study. The lower end was rounded and covered by a thick layer of fibrous tissue. The synovial lining

of the knee was slightly villous in places and was stained brown from blood pigment derived from the old fracture of the femur into the joint. The articular and semilunar cartilages showed no gross abnormalities. Roentgenograms were made of the specimen (fig 8). When these were compared with those of the upper end of the tibia taken twenty months previously, just before amputation of the leg was performed, no change in appearance was detected. The central area of increased density in the upper portion of the diaphysis appeared blotchy in the anteroposterior view, but in the lateral view its central portion was unevenly radiolucent, while the periphery was somewhat circinate in arrangement

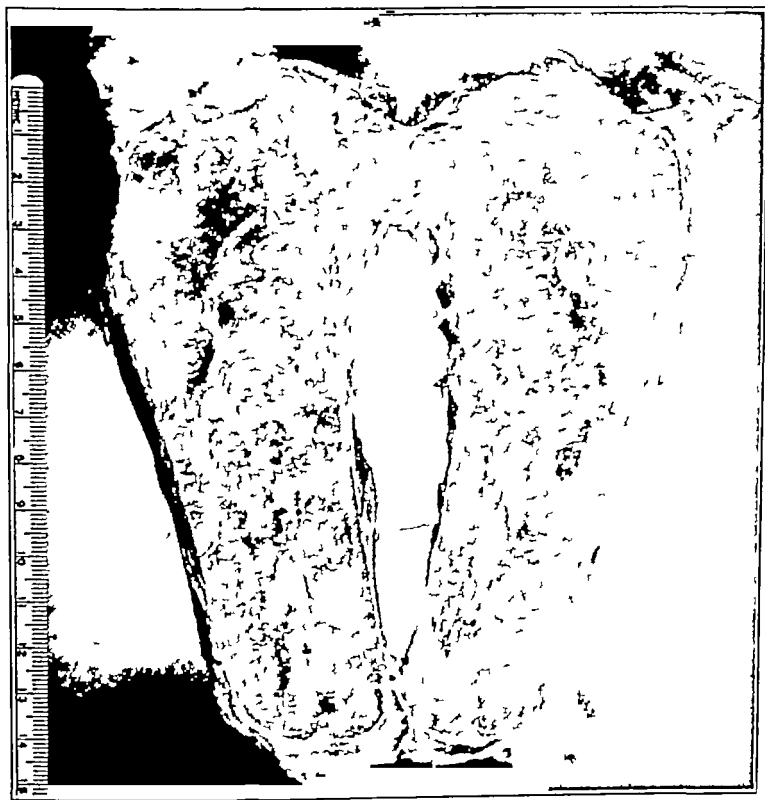


Fig 9 (case 3) —Sagittal section of the amputation stump

and was radiopaque. The shadows of bony trabeculae in most of the area for short distances about were irregularly arranged as if representing new bone which had replaced the old bone. The rest of the bone was reduced in density.

A sagittal section (fig 9) revealed a thin cortex, fine cancellous bone and much fatty gelatinous marrow, indicative of atrophy of disuse. In the center of the upper diaphysis was a mottled irregularly outlined grayish to light yellow area approximately 5.5 cm long by 1 to 2 cm broad. In its upper portion there was a dark necrotic central area about this and extending downward was a yellowish calcified area and external to this was an irregular layer of grayish fibrous tissue. A slice was cut through the involved area of which a roentgenogram was made (fig 10 f). The slice was then decalcified and a microscopic

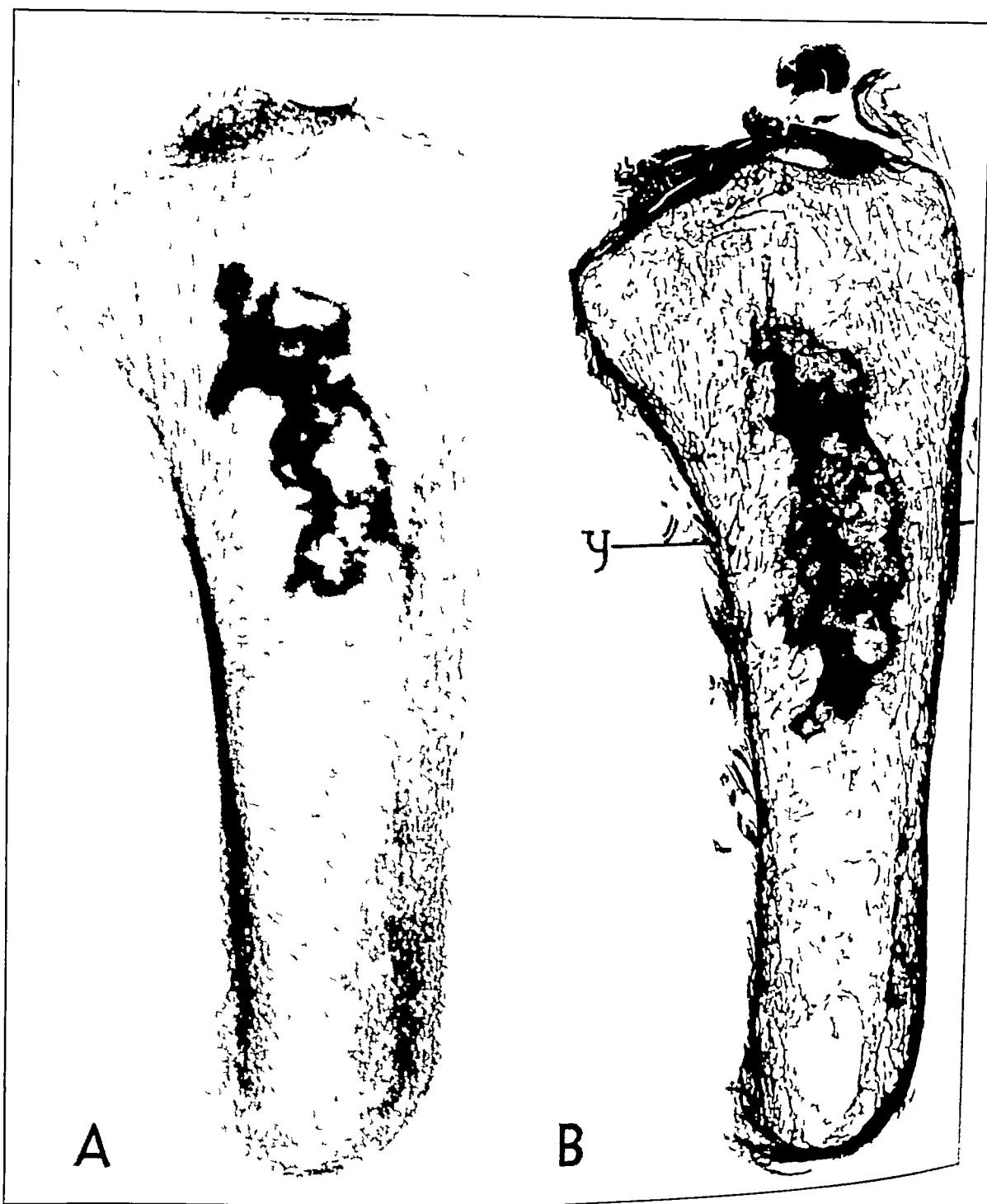


Fig 10 (case 3) —*A*, roentgenogram of a slice of the tibial stump, showing dense shadows cast by the infarct *B*, microscopic section of the stump, showing the infarct



section prepared (fig 10*B*) The central necrotic areas, the calcified intermediary zone and the outer fibrous zone of the involved area and the atrophic rest of the bone are clearly seen

Microscopic examination (figs 11 and 12) revealed the central areas to consist of necrotic bony trabeculae and marrow, with the outline of fat cells still preserved in some regions The intermediary zone showed calcification, some of it calcification of connective tissue, and some, calcification of the necrotic marrow The outer fibrous layer was relatively acellular and shaded over at the periphery into cancellous living bone containing fatty and richly cellular hemopoietic marrow There were numerous arteries and arterioles in the periosteum of the stump, all of which



Fig 11 (case 3)—Photomicrograph ( $\times 8$ ) of the infarct at *y* in figure 10 *a* is living bone, *b* is the fibrous and calcified zone and *c* is the uninvaded portion of the infarct

showed marked to extreme arteriosclerosis with narrowing of their lumens In contrast, there were few arteries or arterioles to be seen in the medullary tissue, and they showed a somewhat lesser degree of arteriosclerosis There was no sign of old thrombosed vessels within the necrotic area The synovial lining showed slight proliferation and tag formation with scattered infiltration with blood pigment The articular cartilage was without notable alterations

The central lesion was an infarct which to judge by the advanced degree of organization, was of many years standing The process of replacement by new bone about the periphery seemed to have come to a standstill

The most plausible explanation is that the lesion resulted from vascular blockage occurring in the early stages of the arteriosclerosis However its ancient

appearance and its stationary character as revealed in roentgenograms separated by an interval of twenty-two months is evidence that it may have developed as a result of an undetermined cause antedating the onset of the arteriosclerosis

Arteriosclerosis of the vessels of the extremities which results in a marked degree of impairment of circulation or in gangrene has received scant consideration as a possible cause of infarction of bone. The studies of Mueller<sup>5</sup> and of Jaffe and Pomeranz<sup>6</sup> showed that a large amount of interstitial aseptic necrosis may be present in the deeper portions of the cortex even at a level considerably higher than that at which the soft

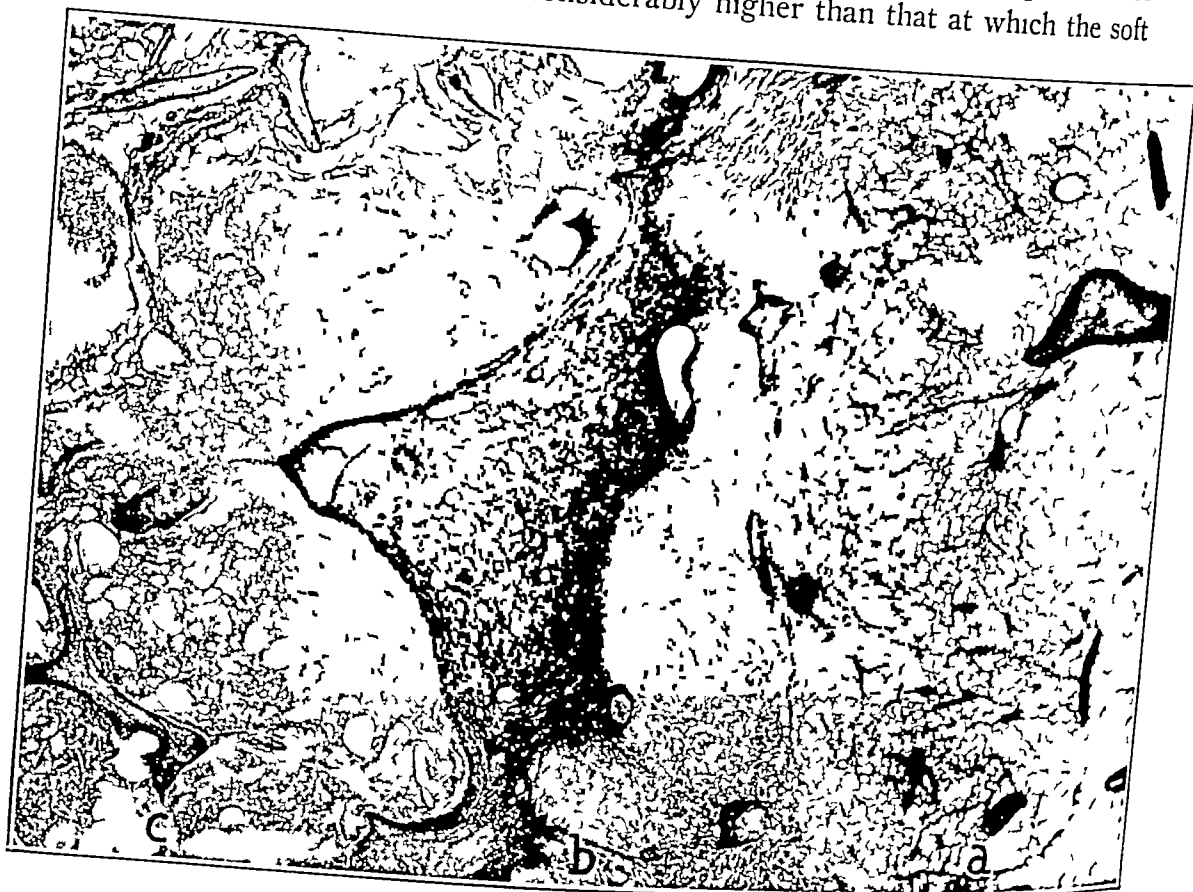


Fig 12 (case 3) —Photomicrograph ( $\times 21$ ) of the right side of the wall shown in figures 10 and 11. *a* is living bone, *b* is the fibrous and calcified zone, and *c* is the uninvaded infarct

parts become gangrenous. The latter authors reported a case of infarction of the posterior part of the body of the astragalus in a 68 year old man who had had circulatory disturbance of the foot for two years and gangrene of the toes for one year. A spreading infection finally neces-

<sup>5</sup> Mueller, W. Ueber das Verhalten des Knochengewebes bei herabgesetzter Zirkulation und das Bild von Nekrose der Zwischenlamellen, *Beitr z klin Chir* **138** 614, 1926

<sup>6</sup> Jaffe, H. L., and Pomeranz, M. M. Changes in the Bones of Extremities Amputated Because of Arteriovascular Disease, *Arch Surg* **29** 566 (Oct) 1934

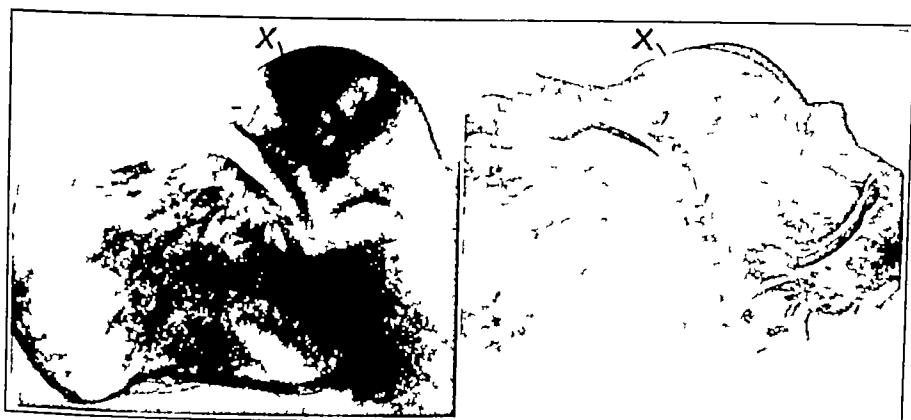


Fig 13—Infarct of the astragalus (1) in a limb amputated because of arterio-sclerotic gangrene (Jaffe's case)



Fig 14—Microscopic section of the infarct in figure 13 surrounded by atrophic living bone

sitated amputation through the lower part of the thigh. Sagittal section of the amputated foot showed the infarct, a photograph, a roentgenogram and a microscopic section of this infarct are reproduced here (figs 13 and 14). Judging by the great difference in density between the infarct and the surrounding atrophic living bone, the cutting off of the circulation of the necrotic area must have occurred at least several months before the amputation. There was spreading acute infection in the vicinity, which, however, did not appear to have influenced the density of the bone. Routine roentgen examination and section of all of the bones of extremities amputated because of arteriosclerotic gangrene should be made for the purpose of establishing the frequency of such circulatory disturbances.

#### BONE INFARCTS AND CHRONIC HYPERTROPHIC ARTHRITIS

The cause of chronic hypertrophic arthritis is still very much in the dark. Pommer considered the primary change to be a degeneration of the articular cartilage resulting from nutritional disturbance and the subsequent changes in both cartilage and bone ends to be due to weight bearing and movement. In some cases the nutritional disturbance is assumed to arise from the trauma of ordinary use in aging or senile cartilage. In other cases changes in the underlying bone are known to precede changes in the cartilage. These are well illustrated in the cases reported here and in part I of chronic arthritis associated with extensive death of epiphyseal bone in fractures of the neck of the femur, dislocation of the hip and caisson disease. This raises the question whether in other cases there are primary changes in the vessels of the subchondral bone, due to other causes, which result in nutritional interference and degeneration of cartilage with subsequent hypertrophic arthritis, since most nutrition of cartilage comes from the underlying bone. The subchondral fibroplasia in the marrow spaces, bone sclerosis and formation of cavities filled with fibrous tissue or fluid which are present in some cases are rarely associated with arteriosclerosis or with obliterative endarteritis of the vessels in the involved region. But small amounts of necrotic bone in the region of absorption and cavitation are occasionally found in microscopic examination. That hypertrophic arthritis and bone infarction may in some cases be due to a common cause is suggested by their association in the following 2 cases.

CASE 4—An obese single woman aged 50, a graduate nurse, had slowly progressive symptoms of pain and some stiffness referable to both knees for sixteen years. She had had painful shoulders during the past four months. She had had no other major illnesses except scarlet fever at the age of 1 year and diphtheria at the age of 30.

She appeared healthy. She weighed 190 pounds (86 Kg). There were slight limitation and pain on motion of both knees and the left shoulder. The knees were slightly swollen and the condylar margins of the femurs were slightly

thickened. The results of physical examination were otherwise without significance. The Wassermann and Kahn reactions were negative. Roentgenograms were made of both knees. A moderate grade of osteophyte formation was present in both knees, most marked at the articular margins of the femurs and the patellas. In the right tibia (fig 15), about 4 inches (10 cm) below the upper end, there was the incidental finding of a centrally situated, irregularly oval shadow of increased density measuring 2 by 3 cm. There was a narrow dense rim about most of its periphery, which was more clearly demonstrated by roentgenograms of less exposure. The shadows of bone for varying distances above

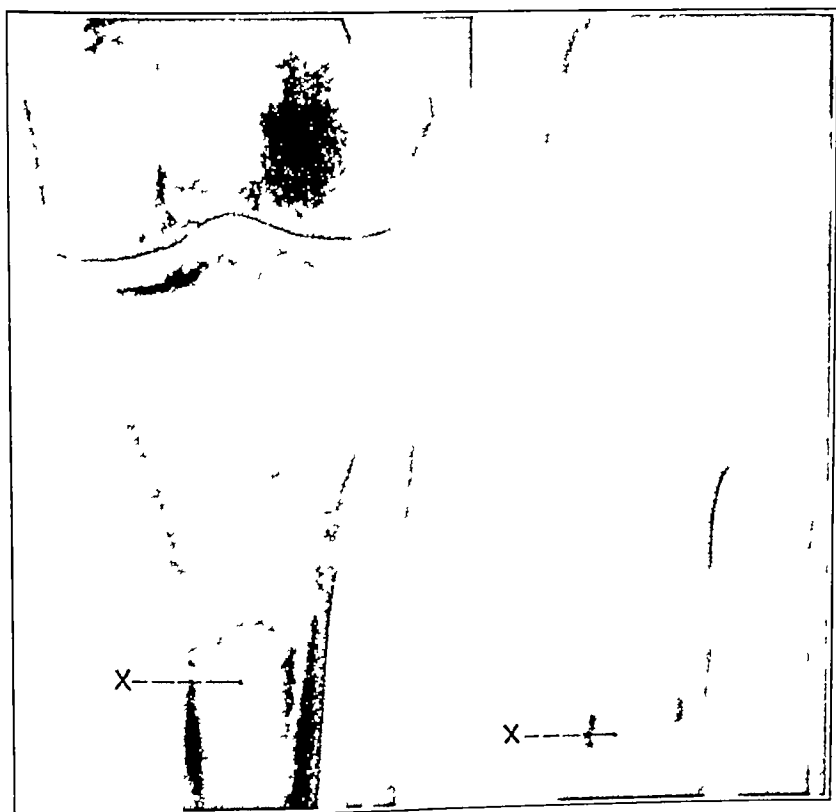


Fig 15 (case 4)—Arthritis of the right knee had produced symptoms for ten years. An old calcified infarct of the tibia (r) had produced no symptoms.

and below were irregularly arranged, which suggested that creeping replacement of dead bone by new bone had gone on at the periphery. The diagnosis was hypertrophic arthritis of both knees and old infarct of the shaft of the right tibia, part of which was organized and the remainder calcified and stationary. On inquiry she stated that there had been no symptoms referable to the seat of the tibial lesion and no history of exposure to compressed air. Roentgen studies were then made of all of the other long bones of the extremities but no abnormalities were noted.

CASE 5—A man aged 55 years a locomotive engineer for eighteen months had had frequent pains in the region of the right shoulder, sometimes radiating

down the arm and forearm, and occasionally pain in the left shoulder and arm. He had been bothered with hay fever for thirty years for which a nasal operation had been performed ten years previously. Otherwise he had suffered only minor ailments.

He appeared healthy. The musculature of the arms and shoulders was well developed. Motion was normal in the shoulders, but elevation of the arms produced pain in both shoulders and extension of the cervical part of the spine caused shoulder girdle pain. The findings were otherwise insignificant. The Wassermann and Kahn reactions were negative.

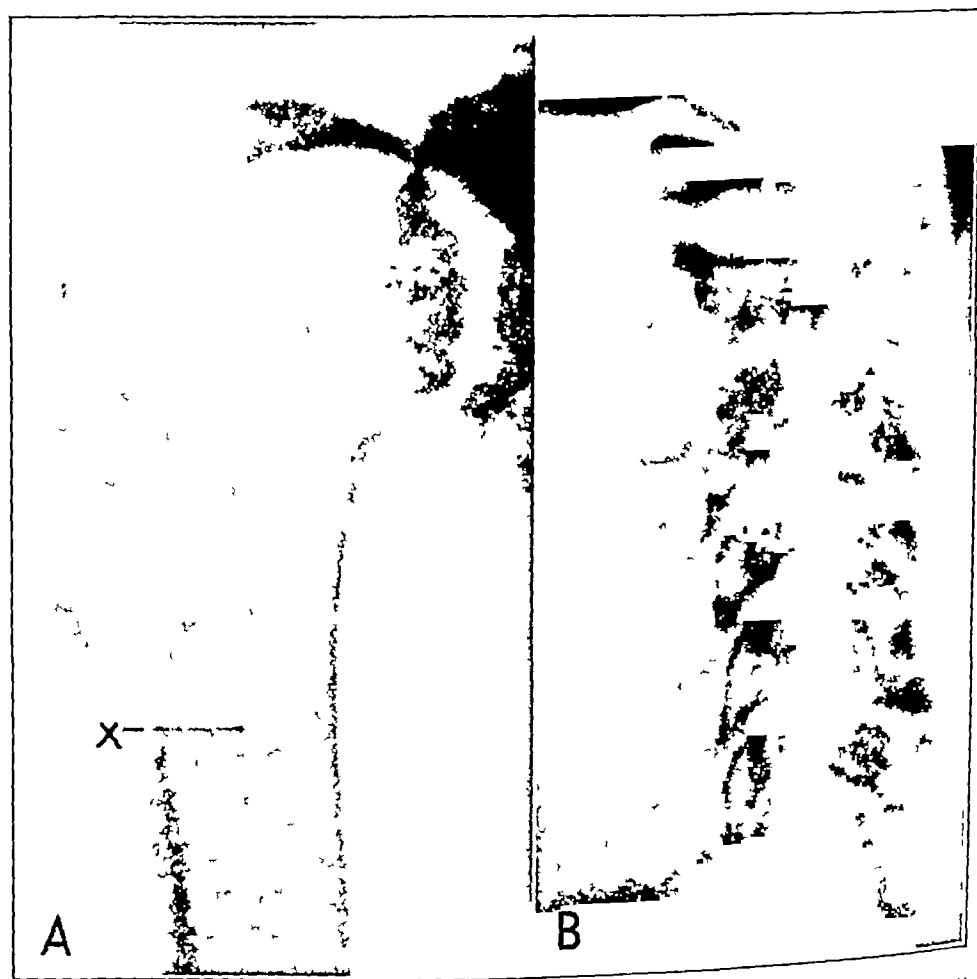


Fig 16 (case 5) —Pains were frequent in the right shoulder and occasionally in the left for one and one-half years. The right humerus (A) shows a dense infarct (x). The cervical part of the spine (B) shows spondylitis with lipping.

Roentgenograms of the spine showed hypertrophic arthritis with lipping, which was marked in the cervical region and slight in the remaining portions. Roentgenograms of the right shoulder showed no changes in the joint, but an incidental finding was a beaded oblong shadow of increased density in the center of the shaft of the humerus, about 4 inches (10 cm) below (fig 16). Roentgenograms were then made of all of the bones and joints of the extremities. Moderate lipping was seen at the articular margins of both hip joints, but otherwise neither the bones nor the joints showed any abnormality. On inquiry the patient told

that he had never worked in compressed air. The diagnosis was hypertrophic arthritis of the spine and hips, compression neuritis of the brachial plexuses, and old calcified infarct of the shaft of the right humerus.

In both cases the infarcts and the arthritis appeared to be of long standing, which is consistent with an etiologic relation.

Lesions similar to that in case 3 and to those of both bones and joints in the presence of caisson disease were reported by Kahlstrom, Burton and me<sup>7</sup> as occurring in 3 cases in which there was no history of work under compressed air, the cause remaining unknown. The remains of the infarcts in the diaphyses were old and calcified and the deforming arthritis, when present, was in an advanced stage. Certain points in the past histories suggested various possibilities such as fat embolism from fractures, the entrance of rheumatic fever and arteriosclerosis, but the case for each remained unproved. Kahlstrom has recently shown me notes on 4 more identical cases (unpublished) of multiple infarcts of bones, in 1 of which infarction followed an attack of caisson disease. A review of some of the standard illustrated textbooks on roentgen diagnosis of diseases of bone reveals roentgen pictures of infarcts that are classified under various other diagnoses.

So-called idiopathic aseptic necrosis in the head of the femur of adults with varying degrees of secondary change in the joint is relatively rare as compared with Legg-Perthes disease in children. Freund<sup>8</sup> first demonstrated the pathologic nature of the disease in 1926 and has subsequently<sup>9</sup> confirmed the findings in 3 other cases. Chandler<sup>10</sup> reported 2 cases proved by operation and pathologic examination in which marked obliteration of arteries of the round ligament appeared to be the cause of the necrosis. A review of the literature on chronic arthritis and that on osteochondritis dissecans of the hip reveals both roentgen and pathologic evidence that such conditions have sometimes been described under those heads. The disease occurs predominantly in men during the early and middle periods of adult life, although in Freund's first case an active stage of the disease was observed in a 77 year old woman. In most cases pain and a limp developed spontaneously and gradually, although in some their onset followed trauma. There was bilateral involvement in 4 of the 6 cases reported by Freund and

7 Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. Aseptic Necrosis of Bone. II. Infarction of Bones of Undetermined Etiology Resulting in Incapacitated and Calcified Areas in Diaphyses and in Arthritis Deformans. *Surg., Gynec. & Obst.* **68**: 631, 1939.

8 Freund, E. Zur Frage des aseptischen Knochennekrose, *Virchows Arch f. path. Anat.* **261**: 287, 1926.

9 Freund, E. Osteochondritis Dissecans of the Head of the Femur. *Arch. Surg.* **39**: 323 (Sept.) 1939.

10 Chandler, F. A. Aseptic Necrosis of the Head of the Femur. *Wisconsin M. J.* **35**: 609, 1936.

Chandler The symptoms in these cases ranged from one to three years in duration and simulated those of chronic hypertrophic arthritis. The roentgen and pathologic pictures resemble those of aseptic necrosis of comparable duration produced by trauma and by other conditions discussed here and will not be elaborated. The arthritic changes were those of the early stages, owing to the comparatively short duration of the disease in these cases.

The following case of bilateral involvement is of special interest in that on one side the head broke down and in six years went through the usual changes, ending with deforming arthritis, while on the other side it retained its form, the necrotic area undergoing reconstruction without the development of arthritis.

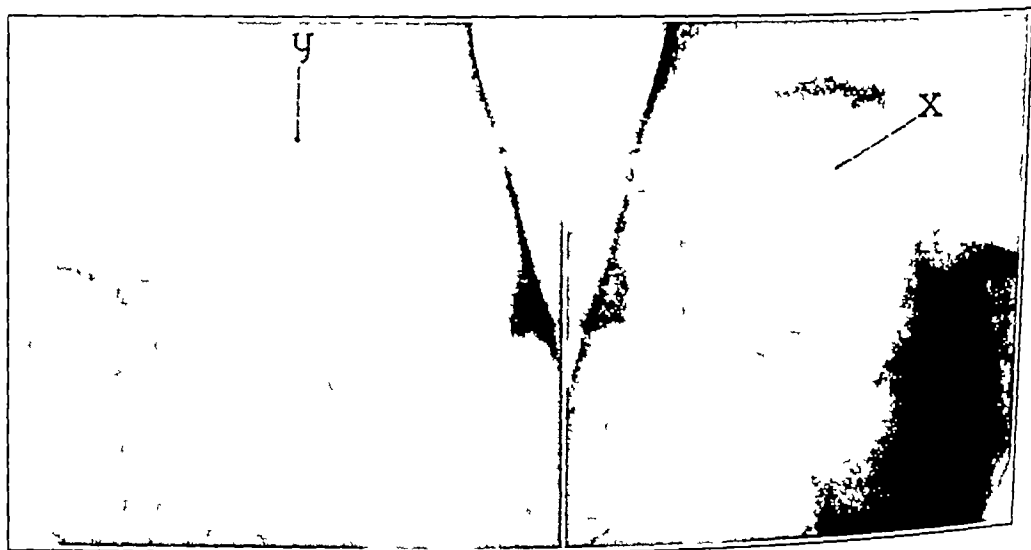


Fig 17 (case 6) —Aseptic necrosis in the head of the femurs, with a depressed sequestrum at weight-bearing portion of the right head (y) and absorption of bone in the left head (x). Dull pain had been present in the right hip for eight months. No symptoms were present in the left hip.

CASE 6—A man aged 27 years, a laborer, complained of pain and weakness in the right hip of eight months' duration, coming on gradually without known cause and progressing slowly. At times he had also had slight pain in the left hip. He had been out of work but had continued to walk. The past history revealed only minor illnesses. The patient was short, well developed and obese. He weighed 170 pounds (77 Kg). He walked with a slight limp in the right leg. The Wassermann and Kahn reactions were negative. The blood pressure was 124 systolic and 78 diastolic. General and regional examinations gave essentially negative results aside from the hips. The right hip showed moderate limitation of abduction and rotation. Flexion was only slightly limited but painful. The left hip was normal.

Roentgenograms revealed changes in the heads of both femurs (fig 17). In the right head there was a break in the articular cortex opposite the acetabular margin, with downward displacement and flattening of the head.



bearing portion mesial to this point. A large area of reduced density was present deep in the head, beneath the point of fracture in the cortex. There was greater density in the head in the flattened region and beneath and mesial to the area of reduced density than in the lateral portion of the head and in the neck. There were faint shadows of osteophytes at the margins of the articular cartilage of the head and at the fovea. In the head of the left femur there was an oval area of slightly reduced density in the same situation as that in the right, with a faint, narrow lateral border of increased density. It was regarded as evidence of an area of bone necrosis and absorption.

Prolonged rest in bed was considered advisable to permit reorganization of the necrotic areas and to insure the least likelihood of collapse of the head of the left femur and of further collapse and arthritis of the right. Economic conditions did not permit this program to be carried out, but the patient was able to lie or sit for the greater portion of the day and went about only for meals and for doing

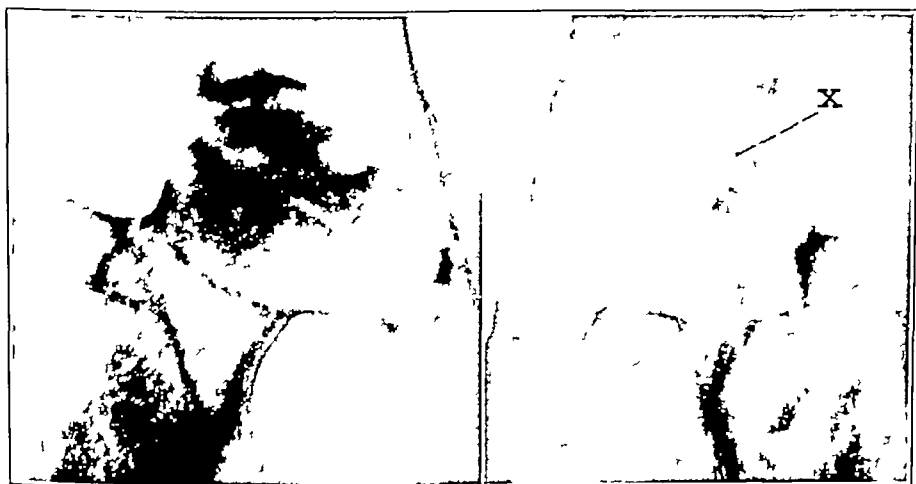


Fig 18 (case 6) —Progression of the lesions two and one-half years after figure 17 was taken. The right hip was continuously painful and stiff. The left hip had lately been slightly painful on extensive use.

chores. He was under observation for five years, and six roentgen examinations were made at intervals of nine to seventeen months. The right hip continued to be painful on use and the limitation of motion remained about the same. The pains in the left hip gradually disappeared, and the joint was free from symptoms after two years. A roentgenogram two and one-half years later (fig 18) showed in the right hip an extension mesially of the absorptive process, with irregular separation of the slightly more depressed and dense weight-bearing portion. There was a blurred area of increased density about the base of the head, extending laterally into the underlying neck. Lipping had increased on the head and was beginning on the margins of the acetabulum. The shadow of the articular cortex of the head below the level of the fovea was very hazy. There was a slight increase in density of the iliac cortex of the acetabulum.

In the left hip the shadow of reduced density in the head had extended mesially to the region of the fovea. It was finely trabeculated and had narrow, irregularly circumscribed borders of increased density. The appearance of the hip otherwise was normal.

The patient gradually became more active during the next two and one-half years, and during the last few months he performed some odd jobs. There was still a dull pain in the right hip on walking but it was less marked than before. A roentgenogram (fig 19) taken five and one-half years after the onset of symptoms revealed in the right hip a mottled alteration in density of the depressed weight-bearing area of the head, indicating invasion by osteogenic tissue and partial replacement by living bone. The lipping of the joint margins was still more marked, as was the sclerosis of the acetabulum. In the left hip the density within the head had returned almost to normal, but the shadows of trabeculae within the old altered area were irregularly arranged and streaked in places, indicating new bone formation throughout.

In this case the indications are that on the right side the necrotic areas within the head included the entire upper portion and that absorptive changes within it so undermined and weakened the weight-bearing por-



Fig 19 (case 6) —Roentgenograms taken twenty-six months after figure 18. The left hip was symptom free and the density of the head restored almost to normal. The right hip was still painful and restricted in motion. The necrotic area (y) was mottled from creeping replacement by new bone.

tion that it caved in. Allison and Wolbach<sup>11</sup> and Axhausen<sup>12</sup> reported similar cases of absorption in the mesial condyle of the femur leading to caving in of the underlying articular cortex and the creation of an osteochondritis dissecans type of loose body. Also, I have seen metastatic carcinoma and Gaucher's disease in the head of the femur lead to the same type of collapse. The results were very slow invasion and incomplete reorganization of the necrotic area and deforming arthritis with

11 Wolbach, S. B., and Allison, N. Osteochondritis Dissecans, *Arch Surg* 16: 1176 (June) 1928.

12 Axhausen, G. Ueber anamische Infarkte am Knochensystem und ihre Bedeutung für die Lehre von den primären Epiphysennekrosen, *Arch f klin Chir* 151: 72, 1928.

permanent impairment of the joint. On the other hand, the central area of necrosis of the left head neither involved the superior portion nor so weakened it that collapse resulted. Consequently, with reorganization of the necrotic area the bone was restored practically to normal, and in the absence of extension of the process to the surface with necrosis of articular cartilage, arthritis deformans was not a sequel.

One feature of case 6, namely, the roentgen evidence of extensive absorption in the necrotic field of each head of the femur, suggests that some factor other than simple blockage of the circulation to the bone may have been active. The area of reduced density in the head of the left femur was not unlike that produced by the fibrous and cystic areas seen beneath the articular cortex of either the head or the acetabulum in cases of chronic hypertrophic arthritis, which again suggests an etiologic relation with that condition.

#### RELATION TO OSTEOCHONDRITIS DISSECANS

Freund regarded the lesions in his case as falling in the category of osteochondritis dissecans. However, there is some difference between this condition and that of the knee and elbow which Koenig designated as osteochondritis dissecans and which has since been repeatedly described for these and various other joints<sup>13</sup>. The following summary of changes is based on a personal experience with the pathologic features of more than 25 cases. In a typical case of osteochondritis dissecans, such as that of the lateral surface of the mesial condyle of the femur, which is by far the commonest site of the disease, a more or less flat oval body consisting of articular cartilage and underlying bone has its bony connections with the epiphysis severed. The cartilage often remains incompletely attached for indefinite periods, while loose fibrous connections are frequently present between the underlying surface of the body and its bed. The amount of bone in the loose body varies in different cases from a layer measuring 1 cm. or more in thickness at its central portion to nothing more than incomplete remnants of the articular cortex. The separated surfaces of both the loose body and its bony bed are found covered by a thin fibrous or fibrocartilaginous layer, and the loose fibrous attachments, when present, connect the two. Roentgenograms show the outline of the bed and also of the bony part of the loose body, whether it remains in situ or is displaced free into the joint.

Microscopic examination reveals evidence which substantiates the view that at the onset of the process there was necrosis of the bone, which, with its overlying cartilage, later became detached. In some cases the old dead bone and marrow are found practically unchanged, or there

<sup>13</sup> Axhausen, G. Ueber den Abgrenzungsvorgang am epiphysären Knochen (Osteochondritis dissecans), *Virchows Arch f path Anat* 252:458 1924.

may be bony detritus filling the marrow spaces, which indicates that use has broken the necrotic bone loose and that friction has produced powdered bone which has early been driven into the marrow spaces. However, if the loose body remains in its bed for some time the bone is usually invaded by blood vessels and fibrous tissue and is slowly replaced in varying degrees by new bone. The articular cartilage suffers varying degrees of nutritional disturbance, but after revascularization of the underlying bone and reestablishment of a source of nutrition by permeating serum the cartilage cells may improve in vitality and staining properties. Judging from roentgen studies, there are cases in which loose bodies become reattached and reorganized, all traces of the lesion eventually disappearing. In cases of complete detachment and of failure of revascularization the deeper portions of cartilage become necrotic and may calcify. But the superficial fibrous layer, as well as the fibrous covering of the bony surface, usually proliferates as a result of nutrition derived from the synovial fluid and forms layers of fibrocartilage, which may calcify.

There are two ways in which the usual type of osteochondritis dissecans differs from the formation of loose bodies associated with massive necrosis and consisting of articular cartilage and bone detached from the articular surface. In the first place, the surrounding bone nearly always appears normal in the roentgenograms, which indicates that all of the bone which became necrotic had been detached, whereas in the cases of massive necrosis of bone bordering on joints of the type observed in case 6 the weight-bearing portion becomes detached while the relatively large remaining necrotic portion undergoes creeping substitution by atypical new bone which is demonstrable in roentgenograms. The previously cited cases of Allison and Wolbach and of Aukhausen are the only ones on record in which there was evidence of extensive involvement of surrounding bone of any sort in a case of osteochondritis dissecans bordering on the knee joint.

In the second place, the loose body in a case of osteochondritis dissecans much less frequently becomes reattached in its bed and invaded and replaced by new bone than does the loose body formed in the presence of massive necrosis of bone bordering on joints. The explanation may be the relative smallness of the body associated with osteochondritis dissecans with its greater freedom for displacement.

The theories as to the etiology of osteochondritis dissecans of the Koenig type are all more or less open to criticism. One theory is that mechanical factors in the form of weight bearing, locomotion and muscular pull bring about, through repeated compression and shearing, a gradual detachment of the most exposed portion of the end of the bone. This is strongly supported by the "microtrauma" experiments of F. L.

schcr,<sup>14</sup> who, working with cadavers, succeeded in detaching bodies of similar size and shape from the lateral surface of the mesial condyle of the femur and from the top of the head of the femur by anchoring the bone of the proximal side of the joint and impacting the articular surfaces thousands of times by means of a revolving motor attached to the bone of the distal side of the joint. Another theory still unsubstantiated is that a single trauma either breaks the chip loose or interrupts the blood supply, after which the body gradually separates from weight bearing and absorption. Axhausen's theory<sup>15</sup> of bland arterial embolism meets with strong objection, especially because of the fact that there are sites of marked predilection without reason why emboli should lodge in those particular locations. Since the disease develops almost entirely during adolescence and in the first third of adult life, it is reasonably certain that arteriosclerosis is not the cause, on the other hand, this age incidence does not exclude the possibility of trauma or of some form of obliterative endarteritis. More experimental and pathologic studies will be necessary for the final solution of this question.

#### NECROSIS OF THE LUNATE BONE

Aseptic necrosis of the lunate bone is so well established that it will not be considered at length. The condition was first described by Kienbock as malacia following a tear of the blood vessels of its dorsal ligaments and nutritional disturbance of the bone. Preisser assumed that the tear of the blood vessels led to simple necrosis of the bone. Then followed the supposition that vascular interruption produced by a painless compression fracture results in necrosis of the bone with subsequent deformity and arthritis. Nagura<sup>16</sup> has recently written in support of this view, basing his claim mainly on the operative finding when the condition is "in full bloom" of a fracture line within the bone, filled with a callus of fibrocartilage. However, I have seen the same fibrocartilage filling the line of separation between the necrotic and the living portion of the head of the femur in cases of necrosis of the head complicating slipped epiphysis. Mueller<sup>16</sup> and Axhausen<sup>17</sup> each regarded the theory of a primary compression fracture as untenable in view of the absence of a history of an injury with pain at the onset and the marked

14 Küntscher G. Ueber das Wesen der mechanisch bedingten Knochen- und Gelenkerkrankungen. *Arch f klin Chir* **193** 665 1938.

15 Nagura, S. Die Pathologie und Pathogenese der sogenannten Lunatummalacie. *Arch f klin Chir* **137** 405 1939.

16 Mueller, W. Ueber die Erweichung und Verdichtung des Os lunatum, eine typische Erkrankung des Handgelenks. *Beitr z klin Chir* **119** 664 1920.

17 Axhausen G. Nicht Malacie sondern Nekrose des Os lunatum carpi, *Arch f klin Chir* **129** 26 1924.

changes in form which eventually ensue. Mueller regarded the cause as undetermined, while Axhausen advanced the theory of bland embolism.

The pathologic process consists of a primary necrosis of practically all of the bone. There follows a certain amount of compression of the cancellous bone, with cloudy increased density visible in roentgenograms. The bone elongates anteroposteriorly, and vascular invasion and replacement of dead bone by new bone soon begin in the anterior and posterior regions, at the points of ligamentous insertion. Roentgenograms may then show small areas of reduced density, and, as the bone is more compressed in its longitudinal axis, fracture lines usually appear, especially running transversely beneath the proximal cortex. The line may be filled with fibrous or cartilaginous callus, and the dead crushed bone meal may be forced into the dead marrow spaces. There may be marked flattening of the bone and increase in density of much of its interior. In other cases absorption of the necrotic bone may lead to a cavitory appearance of the flattened remains. Eventually the necrotic bone is usually replaced by new bone, and the internal structure assumes more nearly the density of normal bone. Articular cartilage undergoes varying degrees of necrosis and absorption, and much of it is replaced by fibrocartilage. Hypertrophic arthritis is often eventually established in the intercarpal and radiocarpal joints. Endarteritis obliterans, such as was present in the round ligament in Chandler's cases of idiopathic necrosis of the femoral heads, has not been reported in association with this condition.

The pathologic picture in the stage of compression and partial absorption and substitution by new bone is illustrated by the following case.

CASE 7—A man aged 20 years, while working as a steam fitter, had an aching pain and slight swelling in the right wrist. There was no history of injury, although his work necessitated much twisting of the wrist. He continued to work, but the condition slowly grew worse, so that after four months he changed to a lighter job. One month later the wrist was still unimproved. Physical examination revealed slight swelling over the front and back of the right wrist in the region of the lunate bone, and on palpation there was a slight boggy feeling in the line of the wrist joint. Motion of the wrist was moderately limited and painful in all directions. There was slight tenderness over the swelling in the region of the lunate bone. A roentgenogram (fig. 20) revealed in the anteroposterior view a slight unevenness and flattening of the proximal articular surface of the lunate bone, the density of which was slightly increased except proximally, where there was an island of reduced density bordering on the wrist joint. In the lateral view the shadow of the bone was increased in its anteroposterior diameter and shortened longitudinally, especially in its dorsal two fifths. There was a line of reduced density suggesting a pathologic fracture. There was no changes in the carpal joints.



Fig 20 (case 7) —Necrosis of the lunate bone five months after onset of symptoms

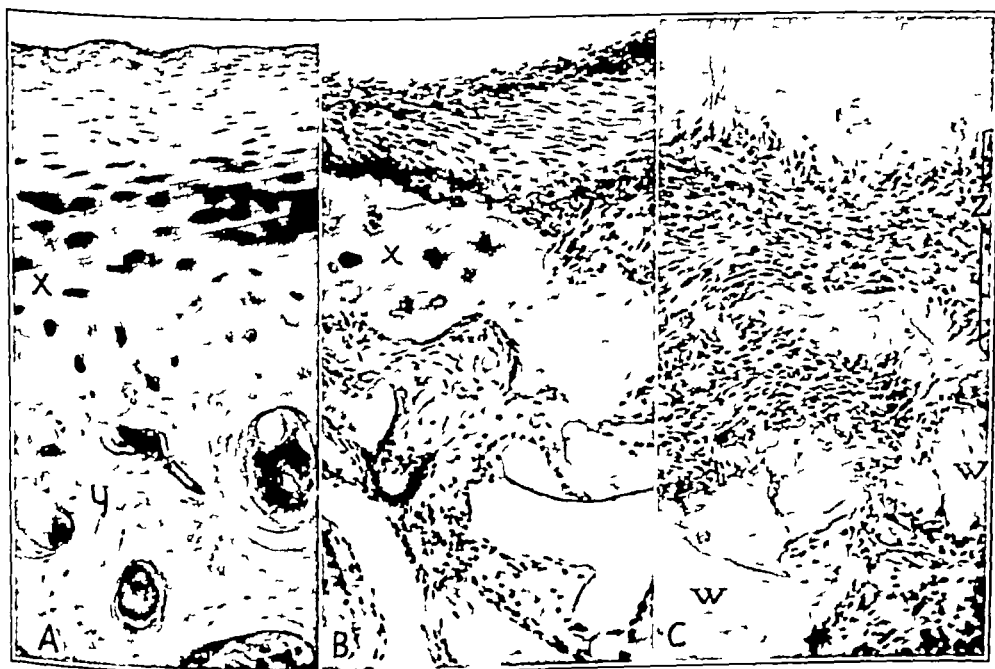


Fig 21 (case 7) —Microscopic sections of the lunate bone removed eight and one half months after onset of symptoms *A* necrotic cortex (*y*) and poorly staining articular cartilage (*x*) *B* zone of transformation The cartilage (*x*) and the bone are being absorbed and replaced by new bone and fibrous marrow *C* dead bone (*w*) being replaced by fibrous tissue (*z*)

Aseptic necrosis of the lunate bone was diagnosed, and subsequently the diseased bone was excised. It was broken into an anterior fragment and a posterior fragment, which were flattened and elongated. Some of the articular cartilage was intact, while other regions had a fibrous overgrowth. The interior of the posterior fragment was mottled gray, with islands of bone interspersed in granulations. The anterior fragment consisted of similar material in its posterior portion, but the anterior part consisted of viable-appearing cancellous bone.

Microscopic sections confirmed the viable nature of the cancellous bone in the anterior portion, the trabeculae of which were irregular and gave the appearance of reconstruction. Sections of the middle and posterior portions showed in some regions the old articular cortex and the spongy bone for a short distance beneath to be necrotic. The overlying articular cartilage was of normal thickness, but its cartilage cells stained poorly and there was calcification in its midportion (fig 21 A). In other regions the articular cortex and the cancellous bone had been absorbed and replaced by very fine living trabeculated bone and fibrous and hemopoietic marrow, while the articular cartilage was extensively necrotic, overgrown and replaced by fibrous tissue (fig 21 B). The interior (fig 21 C) consisted of necrotic bone, some of which had been pulverized in the compression, and fibrous tissue, which in places was absorbing the necrotic trabeculae. There were no vascular changes and very few infiltrative cells to be seen throughout the sections. The changes were those of necrosis of the entire bone with partial invasion and replacement by living bone, partial compression and erosion of trabeculae and partial replacement of necrotic bone by fibrous tissue. The articular cartilage had suffered marked nutritional impairment and in places was being replaced by fibrous tissue. That chronic hypertrophic arthritis was in the process of development was indicated by the beginning lipping of the joint margin of the lower end of the radius, visible in the roentgenogram. The cause of the necrosis remains as obscure as in the case of idiopathic necrosis of the head of the femur in adults, although traumatic factors should perhaps receive the same degree of consideration in the two conditions.

#### SUMMARY

Additional cases are reported of infarction and of secondary arthritis deformans due to blockage of circulation in the bone in adults indicating that the lesion is not uncommon.

Less was determined of the causation of these conditions than is usually determinable in case of infarcts of the viscera or gangrene of the limbs. Caisson disease was the established cause in 1 case, and the nature of the osseous and articular pathologic processes in caisson disease was verified in 1 of the previously reported cases by studies of the head of the femur subsequently removed at operation. Arteriosclerosis was a probable cause in another case. Illustrations are reproduced of an infarct of the talus of a limb amputated for arteriosclerotic gangrene (case of Jaffe and Pomeranz).

In 2 cases an infarct of the shaft of undetermined cause was found associated with multiple hypertrophic arthritis of distant joints, which raised the question of an etiologic relation between the two conditions.



# FAMILIAL OCCURRENCE OF HYPERPLASTIC GASTRIC POLYPS

REPORT OF TWO CASES, CLASSIFICATION OF BENIGN MUCOSAL  
TUMORS OF THE STOMACH

RUDOLF SCHINDLER, M D

CHICAGO

AND

FRANK B McGLONE, M D

DENVER

The purpose of this paper is to report the occurrence of unusual benign tumor growths of the stomach in 2 members of the same family. In these cases the tumors of 2 sisters were removed surgically. The lesions were found to be histologically similar polypoid growths.

## REPORT OF CASES

A 49 year old woman was seen by Dr James I Baltz of Detroit on Sept 9, 1939. The history was that of epigastric distress of ten years' duration. The distress was described as a burning sensation not related to meals and occasionally relieved by administration of alkalis or change of position. There had been no loss of weight. For the past year the patient had noticed some numbness and tingling of the hands. The mother of the patient had died at the age of 64 with carcinoma of the colon. An older sister of the patient had had a gastric tumor removed in 1929 at Philadelphia. Sections of this tumor were obtained and will be described later. On physical examination there were no positive abnormalities. The stools contained no occult blood, there was no anemia, and the gastric contents contained free hydrochloric acid. Roentgen examination revealed nothing conclusive. An irregularity of the lesser curvature was noted, but no definite diagnosis was made.

*Gastroscopic Examination*—This was first made by Dr James I Baltz on September 14, at which time he made the following observations: at depth III with the button at 7 o'clock (greater curvature at the upper portion of the fundus) there was an area apparently 4 to 5 cm in diameter where the mucosa was thrown into moderately heavy folds, here there were redness and swelling, but no bleeding was seen, the appearance was that of mild hypertrophic gastritis.

About a month later (October 6) the patient was again studied gastroscopically by Dr Baltz, who found the picture changed. There was less reddening of the mucosa. Several heaped-up, small, apparently polypoid areas were seen, these were roughened but not bleeding. At this time the diagnosis of polyposis of the stomach was made and was discussed with the patient.

On October 13 the patient was seen by one of us (R S). A very unusual lesion of the posterior gastric wall was seen gastroscopically. In depth II (mid-portion of the stomach) some folds of the greater curvature and posterior wall

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From the Department of Medicine, the University of Chicago

2 to 4 cm long were seen, they were branching but completely stiff and had a beady, nodular appearance. In depth III (upper portion of the stomach) a huge foldlike protrusion (fig 1) was observed which flattened out toward the cardia. This was entirely stiff and appeared to be infiltrated, and many surface nodes were seen. Mucosal hemorrhages, especially in the portion toward the lesser curvature, were noticed.

On November 15, examination with the gastroscope was again made. At this time the lower and upper ends of the lesion were seen, and there was definitely no sharp limit at any side. There was less bleeding at this time, but otherwise the picture was the same as that seen on the first examination. It was felt that this was a case of tumor-forming gastritis, but an infiltrating carcinoma could not be ruled out. A laparotomy with removal of a biopsy specimen from the upper posterior wall was suggested.

On November 30, a laparotomy was performed by Dr. Alexander Brunschwig. When the peritoneum was opened and the stomach examined manually, the tumor growths could not be felt, and the stomach was opened. The upper posterior wall of the stomach presented a markedly hypertrophic appearance. In this region polypoid masses could be seen. These were removed digitally, much as one would

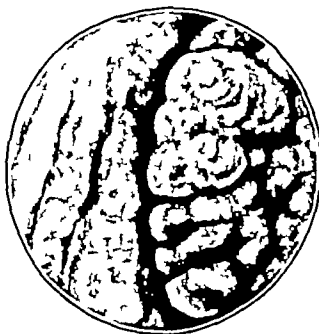


Fig 1—Gastroscopic picture of a hyperplastic polyp. A huge foldlike protrusion is seen. This fold is entirely stiff and appears infiltrated, many surface nodes are visible. Two granular folds are visible in the mucosa to the left of the stomach.

pluck individual grapes from a bunch. A section of the anterior wall of the stomach was excised for histologic study.

Microscopic examination of the excised portion of the anterior wall revealed normal mucosa. This was in accord with the gastroscopic picture of the anterior wall.

The polypoid masses presented an unusual histologic appearance. The subdivisions of the growth (figs 2 and 3) were bordered by large complex crypts, and the epithelium of the peripheral zone was variable. In the vicinity of the muscle and connective tissue core there were many cystic glands between the hyperplastic surface layer and the stalk. The majority of the glands, however, were not unlike those of the normal gastric wall except that many of them were slightly dilated. Body chief (zymogenic) and parietal (acidophilic) cells appeared in normal proportions.

The appearance of different portions of the growth was varied, nevertheless there were no glands which appeared imperfect or frankly neoplastic. There was no evidence of any invasion of the stalk. In the growth there were areas of

sutial inflammation, the predominant cells were lymphocytes and plasma cells, but eosinophils and neutrophils were numerous in some areas

The section of the tissue taken from the sister ten years previously showed a similar type of tumor, although from a different portion of the stomach

This section (figs 4 and 5) represented a portion of a mucosal tumor covered by mucosa which closely resembled that of the adjacent pyloric wall. The stalk was composed of smooth muscle (connected with the muscularis mucosae), blood vessels and connective tissue, which was continuous with the submucosa. On the summit of the polypoid growth the branching prolongations of smooth muscle were thin. The gastric glands covering the stalks had the character of pyloric

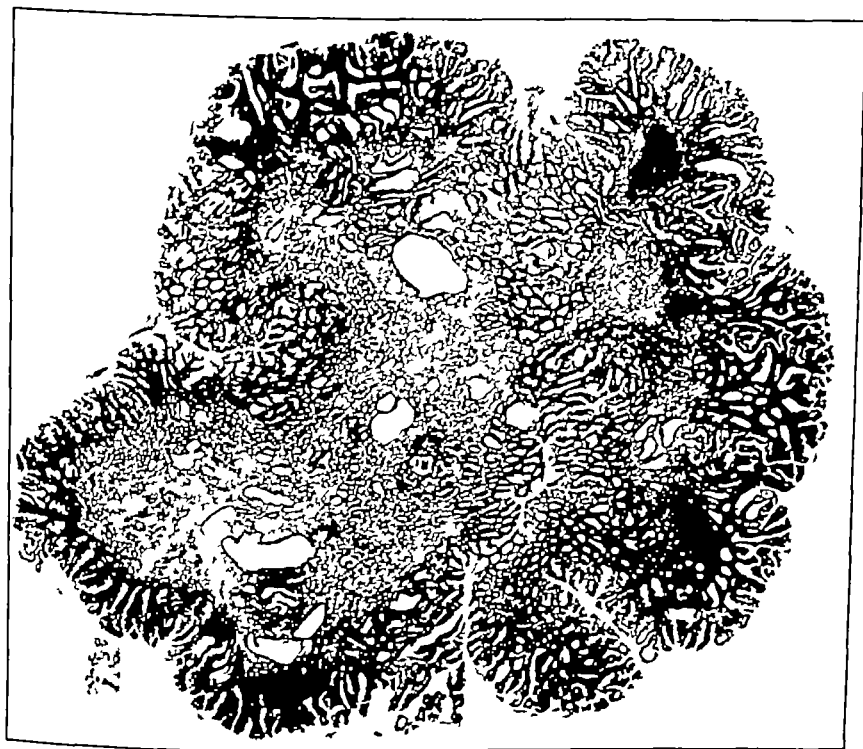


Fig 2—Hyperplastic polyp. The photomicrograph shows a cross section of one of the tumors seen in fig 1. This polyp was located in the posterior gastric wall, near the cardia. Note the lack of inflammatory reaction throughout the polyp.

glands, with large mucous crypts near the surface and with small glands of the Brunner type at their base. There was very little difference between the Brunner type glands in the polyp and those in the adjacent wall. There were several dilated glands located close to the stalks. No unusual mitotic activity was noted. There were numerous interstitial cells in the papilloma and the adjacent mucosa. These consisted chiefly of plasma cells with some eosinophils and a few neutrophils. The mucosa of the adjacent wall contained a few groups of lymphocytes in follicular formation and there was a little perivascular infiltration of round cells in the outer layers of the muscular coat of the stomach. No inflammation of the submucosa was seen except in the stalk of the papilloma.

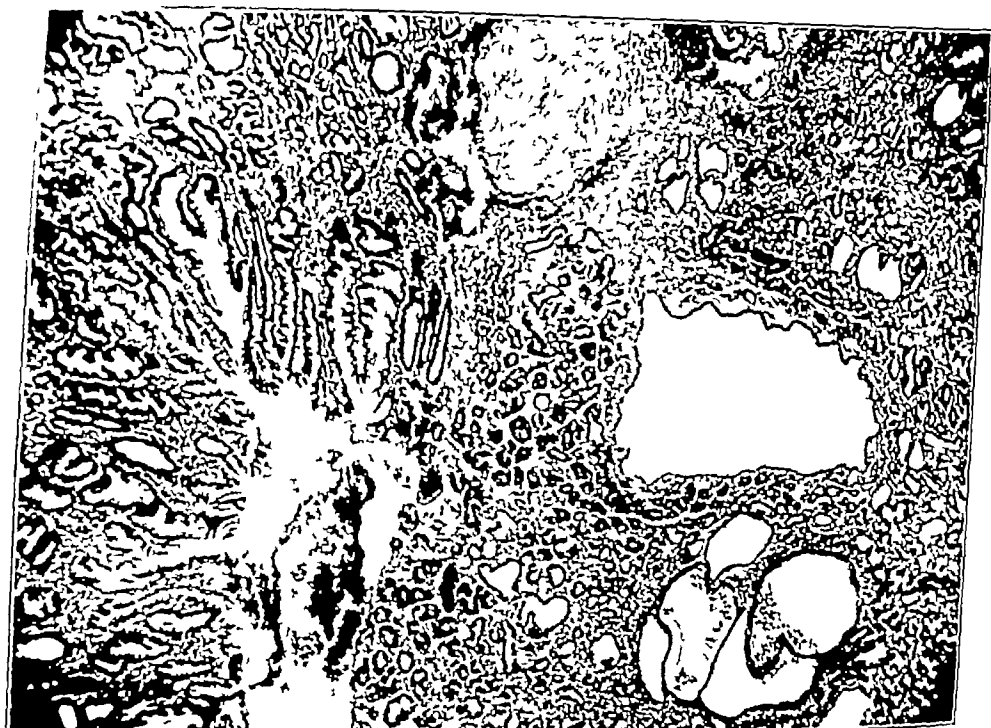


Fig 3—Higher magnification of a portion of the polyp seen in figure 2. Large complex crypts can be seen, and at the left a portion of the hyperplastic surface layer is visible. In the center and to the right the glands are of the type normally seen in the cardiac portion of the stomach.

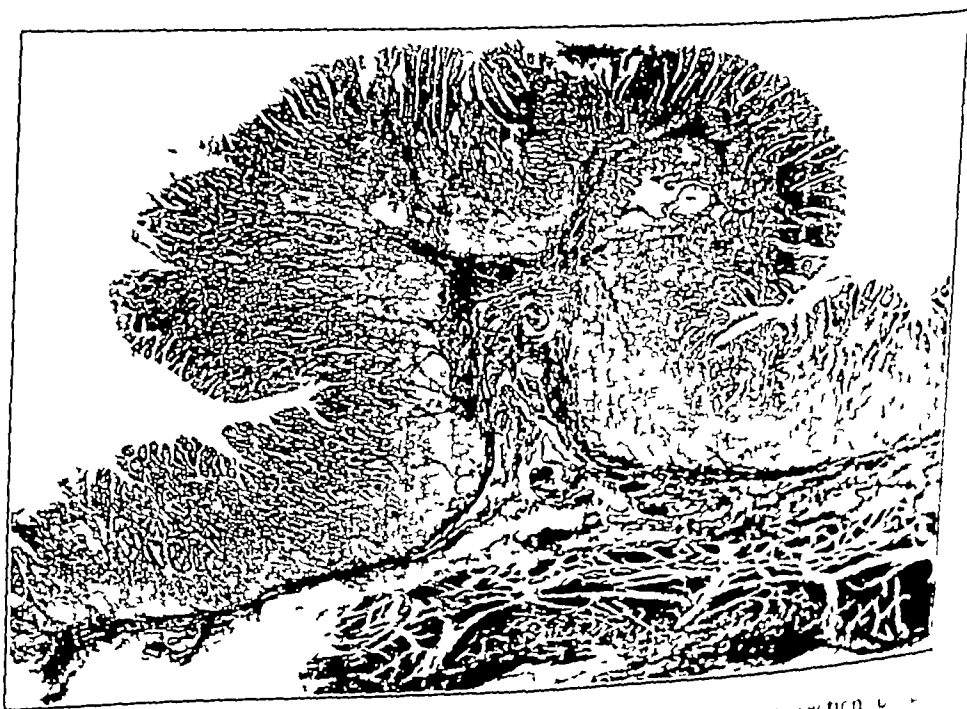


Fig 4—Hyperplastic polyp. The photomicrograph shows a section of a gastric tumor taken from the sister of the patient whose tumor is shown in figures 2 and 3. The polyp is composed of a smooth muscle stalk covered with hyperplastic mucosa. This tumor was located near the pylorus.

As seen microscopically, these growths were not true adenomatous polyps. They were hyperplastic growths of the gastric mucosa forming intragastric tumors. Such growths are very rare.

## COMMENT

Classification of polypoid growths of the gastric mucosa is not easy, as these lesions are not common, and abundant histologic material is not available. This is in contrast to conditions in the intestine, where such

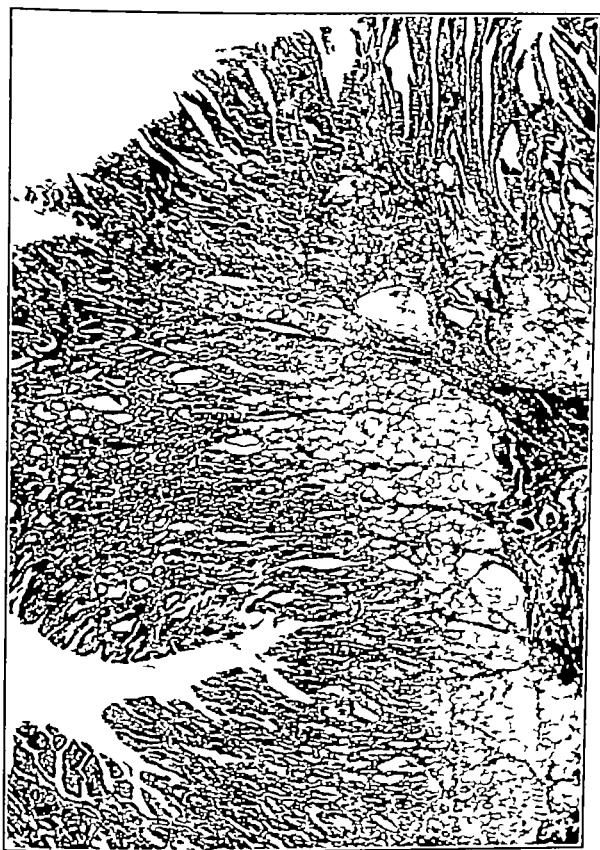


Fig 5—Higher magnification of the gastric wall and the edge of the polyp seen in figure 40. The gastric glands covering the stalk have the character of pyloric glands with small glands of the Brunner type at their bases. There is little difference between these glands and those of the adjacent pyloric mucosa. No evidence of inflammation is seen.

formations are frequently observed<sup>1</sup>. However, with the advent of roentgen relief technic and gastroscopy, it has become obvious that

<sup>1</sup> Klemperer, P. Studies in Adenomatous Polypi and Carcinoma of the Colon, *Tr. Am. Gastro-Enterol. A.*, 1938, p. 88.

gastric polypoid growths are not so rare as was formerly thought. In 1936, Lawrence,<sup>2</sup> in 7,000 autopsies at the Cook County Hospital, observed 50 cases of gastric polyps (0.7 per cent), in 9 of which the lesions were malignant. In a series of 1,000 cases in which gastroscopic study was made by one of us (R. S.<sup>3</sup>), 22 cases of benign tumors were observed. Twenty (2 per cent) were benign epithelial tumors.

Even though polypoid growths of the stomach are seen much less frequently than those of the intestine, their study is easier. The many extensively ulcerative inflammations of the intestine, such as ulcerative colitis, regional ileitis and other conditions which may lead to the formation of inflammatory growths, are not seen in the stomach, although a rare form of ulcerative atrophic hyperplastic gastritis of the antrum does occur. It is possible, therefore, to make a more clearcut definition of the types of mucosal growths in the stomach.

In accordance with the present knowledge of polypoid growths of the gastric mucosa, these may be divided into three groups: (1) inflammatory pseudopolyps, which originate as compensatory formations in the presence of chronic atrophic gastritis, (2) true adenomatous polyps, and (3) hyperplastic polyps.

It cannot be stated whether transitions between these groups occur. In the discussion to follow, these groups will be considered according to (a) gross and microscopic appearance, (b) possible hereditary factors, (c) relation to carcinoma and (d) differential diagnosis.

#### GROSS AND MICROSCOPIC APPEARANCE OF THE THREE TYPES

1. As has been noted, severe atrophic ulcerative gastritis leading to the formation of inflammatory pseudopolyps is rare. This disease has been studied especially by Konjetzny.<sup>4</sup> Grossly the inflammation often is restricted to the antrum. Thick nodes of different size cover its mucosa, and between these shallow ulcerations are visible. Microscopically (fig. 6) the mucosa is thoroughly atrophic. The shallow ulcerations do not penetrate the muscularis mucosae, but severe inflammatory infiltration is seen even in the deeper layers of the gastric wall. The nodes consist chiefly of connective tissue containing numerous plasma cells, apparently representing an attempt on the part of the tissues at regeneration. They may contain atypical tubules, however.

<sup>2</sup> Lawrence, J. C. *Gastro-Intestinal Polyps. Statistical Study of Mahomet*. *Am J Surg* **31**: 499, 1936.

<sup>3</sup> Schindler, R. *The Incidence of the Various Types of Gastric Disease Revealed by Gastroscopic Study*, *Am J M Sc* **197**: 509, 1939.

<sup>4</sup> Konjetzny, G. E. *Ueber die Beziehungen der chronischen Gastritis zu den Folgeerscheinungen und des chronischen Magensulkus zur Entwicklung des Magenkrebesses*, *Beitr z klin Chir* **85**: 455, 1913.

their structure is so definitely inflammatory that they can scarcely be mistaken for true tumors

2 True adenomatous polyps These represent the most common type of benign gastric tumor Adenomatous polyps are frequently solitary, but they may be multiple Often they are seen with atrophic gastritis (especially in persons with pernicious anemia), which may be the soil for this growth They are either broad based or pedunculated



Fig 6—Microscopic section of an inflammatory pseudopolyp The glandular apparatus of the mucosa has disappeared, the mucosa is atrophic, containing many cysts of the gastric crypts and compensatory proliferation of the surface epithelium The polypoid growth contains some atypical tubules but consists chiefly of inflammatory granulation tissue Note the severe inflammatory invasion of the muscularis mucosae.

but always are sharply limited from the surrounding mucosa, their red color often is contrasted with the grayish pink of the surrounding atrophic mucosa Apical ulceration may occur, but this ulceration does not prove malignancy Histologically (fig 7) these polyps consist

entirety of glandular tubules which present a dedifferentiated, though very regular, epithelium. Between the tubules some inflammatory cells may be observed.

3. *Hyperplastic polyps*.—Although hyperplastic formations in the intestine seem to be frequent,<sup>5</sup> we have not found in the literature other cases of true hyperplastic polyp formation in the stomach. Grossly these polyps are not sharply defined, they blend with the surrounding mucosa, which appears swollen. The folds are thickened, stiff and beady or partly covered by small granules, which apparently are the first stage of the polyp formation.

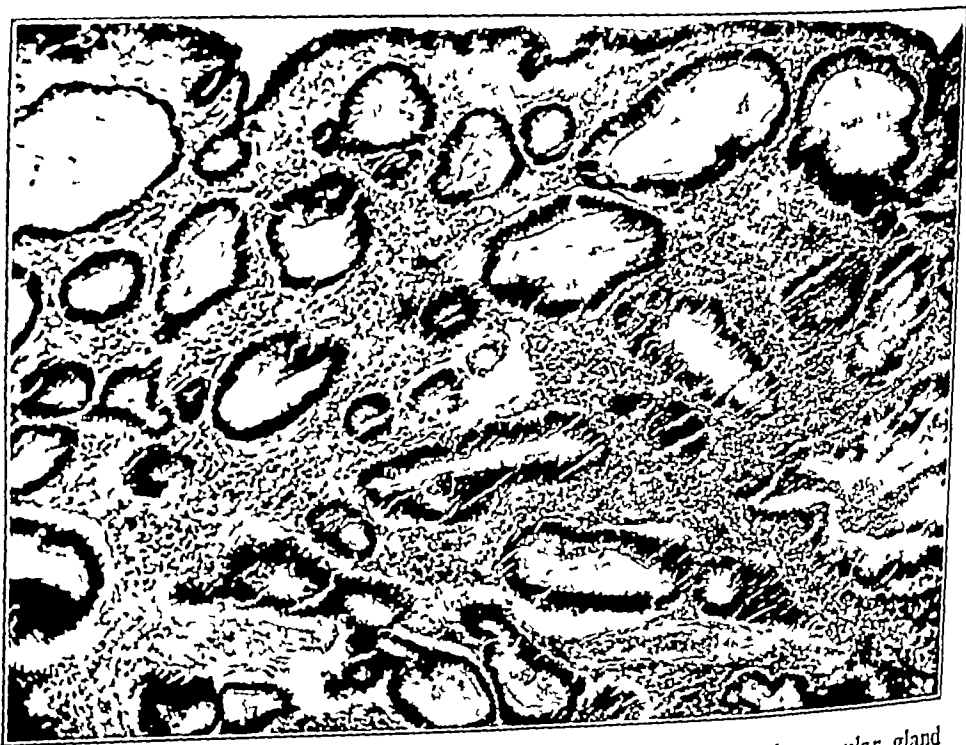


Fig. 7.—Photomicrograph of an adenomatous polyp, showing the regular gland like arrangement. There is little inflammation, and the tubules are not typical gastric glands.

Microscopically (see figs. 1, 2 and 3) the nodes consist of hyperplastic gastric mucosa, the elements of which are well differentiated. It is important to note that these growths contain the specific elements of the surrounding mucosa. This is well shown in our 2 cases, one polyp was from the upper portion of the posterior wall, showing chief cells and acidophilic cells in correct proportions. The other was a prepyloric growth and contained pyloric cells and Brunner's glands. Some inflammatory reaction was present, but it was very slight. No atrophic

5. Barger, R. J., and Coffey, J. A. *Intestinal Polyps*. Pathogenesis and Relation to Malignancy, Surg., Gynec. & Obst. 69: 136, 1939.



changes were seen, and the mucosa from a portion of the stomach remote from the lesion was normal

#### HEREDITARY FACTORS

Familial occurrence of intestinal polyps is well known,<sup>6</sup> but some observers<sup>7</sup> have stated that gastric polypoidosis, in contrast to colonic polypoidosis, has no definite hereditary factors. There is no definite evidence to show any familial tendency of the first two types of gastric polypoid growths (pseudopolyps and adenomas). In this paper, however, we have presented 2 cases of a third group (hyperplastic polyps) which occurred in 2 sisters. This familial occurrence should not be considered a mere coincidence, as this condition is extremely rare. This observation seems to show that at least in the hyperplastic polypoid formations of the stomach there may be a definite heredofamilial tendency.

#### RELATION TO GASTRIC CARCINOMA

1 *Pseudopolyps*—Konjetzny<sup>8</sup> has shown transitions from gastritis to polyp to carcinoma. There can be little doubt that atrophic gastritis with compensatory inflammatory nodes may in some cases lead to carcinoma.

2 *Adenomatous Polyps*—Solitary or multiple adenomatous polyps arising from atrophic gastritis are generally believed to be precancerous lesions. When multiple benign adenomas are found, one of which shows carcinomatous degeneration, a definite relation can scarcely be doubted.<sup>9</sup> Miller and his associates<sup>10</sup> reported cases of adenomatous polyp in which carcinomatous degeneration was observed. It seems, however, that the gradual development of a certainly benign tumor into carcinoma has not yet been observed clinically. In 1 case of our own observation<sup>11</sup> a small filling defect was observed at roentgen examination three years before surgical removal of a polypoid carcinoma grow-

6 Tønnesen, H. Polyposis Gastrointestinalis, *Acta chir Scandinav* **68** (supp 17) 1, 1931. Wechselmann, L. Polyp und Carcinom im Magen-Darmkanal, *Beitr z klin Chir* **70** 855, 1910. Lockhart-Mummery, P. Cancer and Heredity, *Lancet* **1** 427, 1925.

7 Brunn, H., and Pearl, F. Multiple Gastric Polyposis, *Am J Surg* **40** 51, 1938.

8 Konjetzny, G. E. Beziehungen der chronischen Gastritis zum Magenkrebs, *Verhandl d deutsch Gesellsch f Chir* **43** (pt. 1) 65 1914.

9 Menetrier, P. Des polyadenomes gastriques et de leurs rapports avec le cancer de l'estomac, *Arch de physiol norm et path* **1** 236, 1883.

10 Miller, T. G., Elason, E. L., and Wright, V. W. M. Carcinomatous Degeneration of Polyp of the Stomach, *Arch Int Med* **46** 841 (Nov) 1930.

11 Schindler, R., and Gold, R. L. Gastroscopy in Early Carcinoma Surg Gynec & Obst **69** 1 (July) 1939.

ing in an atrophic mucosa. It is not certain that three years is a long enough period to prove the benign nature of the growth at the time of its origin.

3 *Hyperplastic Polyps*—Nothing is known about the relation of the hyperplastic polyp to carcinoma. One of our patients, operated on ten years ago, is living and well at present, and the other patient, operated on in November 1939, is living and gaining weight. It is notable, however, that the mother died of carcinoma of the colon, although this could be purely coincidental. It should be remembered, however, that hyperplastic changes in the intestine have a definite relation to carcinoma.<sup>5</sup>

#### DIFFERENTIAL DIAGNOSIS

1 The correct diagnosis of the inflammatory formation of pseudopolyps is difficult. However, the roentgen picture of round, regular filling defects together with narrowing of the antrum may suggest this form. At gastroscopic examination the differential diagnosis between pseudopolyps and infiltrating carcinoma with superficial ulcerations seems to be impossible.

2 The true adenomas are easily diagnosed gastroscopically. The picture is characteristic, consisting of red elevations covered by mucosa on the background of the thinned, grayish, atrophic mucosa. The elevations are pedunculated or broad based and rarely ulcerated. The picture is typical and not likely to be mistaken. The diagnosis of early carcinomatous change may be difficult, however, this remains to be seen. At roentgen examination small, round, sharply defined filling defects are sometimes seen. For the diagnosis of small adenomas gastroscopic study is the superior method.

3 The differential diagnosis of the third type, the hyperplastic polyp, has proved unexpectedly difficult. The first observer in our case (Dr Baltz) diagnosed hypertrophic gastritis of the posterior wall on his first examination but later saw and described with eminent correctness the origin of benign tumors in this area. When one of us (R. S.) examined the patient the tumors could no longer be discerned. They had grown so closely together and so close was the connection between them and the surrounding hyperplastic mucosa that tumor simulating gastritis and carcinoma were the only diagnoses considered.

#### SUMMARY

In 2 sisters, hyperplastic polyps originating from a hyperplastic mucosa were found. The lesions were located in 1 case in the upper portion of the posterior wall of the stomach and in the other in the pyloric antrum. The microscopic picture of these formations is described.

Comparison of these lesions with other polypoid growths of the stomach leads to a division of gastric polypoid growths into three groups (1) inflammatory pseudopolyps, (2) adenomatous polyps, and (3) hyperplastic polyps

The gross and microscopic pictures of the three groups are described. The possible role of hereditary factors, the relation to carcinoma and the differential diagnosis are discussed.

The first patient was referred to us by Dr James I Baltz, who also reported the clinical data. The material in the case of the second patient was supplied by Dr John H Gibbon Jr and Dr John Bauer, pathologist at the Pennsylvania Hospital in Philadelphia. The study and description of the microscopic sections are the contribution of Dr Eleanor M Humphreys.

# COMPARATIVE CONCENTRATION OF HUMAN HEPATIC BILIRUBIN AND CHOLESTEROL BY THE GALLBLADDER

A POSTMORTEM STUDY

SAMUEL J LLOYD, M D  
Fellow in Surgery, the Mayo Foundation  
ROCHESTER, MINN

Many studies on bile and its constituents have been made in the past. Most of these have been directed simply to determining the absolute amounts of the various constituents. In man, these studies have been of three types: (1) on gallbladder bile taken at operation, (2) on bile taken postoperatively from a hepatic fistula, and (3) on gallbladder bile taken post mortem. Comparisons have been made between the first and second and between the second and third types of determination. That any of the determinations are truly physiologic may be debated—the very fact that operation on the biliary tree was required impugns the validity of the results. McNee<sup>1</sup> pointed out that most results and methods are unsatisfactory. The present study differs from the former ones in that the hepatic bile used for these determinations was taken at the same time as the gallbladder bile in cases in which operation on the biliary tree had not been performed and in which the gallbladder and the liver were grossly normal.

There is a second group of determinations in the literature, on experimental animals. These were taken more or less simultaneously, and comparisons were made. However, man is the only animal in which cholesterol stones are common, particularly in the aged.<sup>2</sup>

The objective in this paper is to compare the concentration of hepatic cholesterol by the gallbladder with the concentration of hepatic bilirubin by that organ. The analyses were all done on specimens obtained post mortem. It is hoped that by these comparisons it will be possible to determine whether the gallbladder decreases by absorption, increases

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Work done in the Section on Pathologic Anatomy, and the Division of Biochemistry, the Mayo Clinic

1 McNee, J. W. Cholesterol. An Account of Its Relations to Pathology and Physiology, *Quart J Med* 7 221-236 (April) 1914

2 Mentzer, S. H. A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, *Surg, Gynec & Obst* 42 782-793 (June) 1926

by secretion or simply concentrates the hepatic cholesterol which is delivered to it. Besides this, certain factual data will be presented for the first time. Only two references can be found relative to determinations on postmortem hepatic bile.<sup>3</sup> Newer and more delicate quantitative analyses now make these determinations feasible, though they are still difficult and frequently subject to error that is too great.

#### REVIEW OF THE LITERATURE

Various investigators have made determinations of the quantities of cholesterol and bilirubin in hepatic and in gallbladder bile. Many of these figures antedate satisfactory experimental or clinical methods, but even recent workers have obtained widely varying results. The values for hepatic bilirubin obtained by various investigators vary from 115 to 128 mg per hundred cubic centimeters.<sup>4</sup> Those for hepatic cholesterol vary from 0 to 232 Gm per hundred cubic centimeters.<sup>5</sup>

A similar situation is evident on study of the determinations found in the literature for gallbladder bilirubin and cholesterol. The quantities of bilirubin vary from 3.5 mg per hundred cubic centimeters for healthy normal subjects to as high as 1,786 mg per hundred cubic centimeters.<sup>6</sup>

3 (a) Elman, R., and Taussig, J. B. The Cholesterol Function of the Gall Bladder, *J. Exper. Med.* **54** 775-787 (Nov.) 1931. (b) Fox, F. W. The Composition of Human Bile and Its Bearing upon Sterol Metabolism, *Quart. J. Med.* **21** 107-121 (Oct.) 1927.

4 (a) Antic, D., and Goropevsek, M. Cholesterin und Bilirubin in der Galle und ihr diagnostischer Wert, *Arch. f. Verdauungskr.* **61** 334-343, 1937. (b) Elton, N. W. Bilirubin Concentrations in the Human Gallbladder, *Am. J. Clin. Path.* **6** 81-90 (Jan.) 1936. (c) Greene, C. H., Walters, W., and Frederickson, C. H. The Composition of the Bile Following the Relief of Biliary Obstruction, *J. Clin. Investigation* **9** 295-310 (Dec.) 1930. (d) Newman, C. Physiology of the Gall-Bladder and Its Functional Abnormalities. I. Physiology, *Lancet* **1** 785-791 (April 15) 1933, II Disorders of Motility, *ibid.* **1** 841-848 (April 22) 1933, III Abnormalities of Concentration and Secretion in the Gall-Bladder, *ibid.* **1** 896-901 (April 29) 1933. (e) Rosenbloom, J. A Quantitative Chemical Analysis of Human Bile, *J. Biol. Chem.* **14** 241-244, 1913. (f) Schöndube, W., and Kalk, H. Ueber moderne Methoden in der Diagnostik der Gallenblasenerkrankungen, *Med. Klin.* **21** 1949-1952 (Dec. 24) 1925. (g) Elman and Taussig.<sup>3a</sup>

5 (a) Bockus, H. L., and Eiman, J. Experimental and Clinical Significance of the Cholesterol Content of the Bile, *Arch. Int. Med.* **34** 161-167 (Aug.) 1924. (b) Bronner, H. Wasserstoffionenkonzentration der Galle und Steinbildung, *Arch. f. klin. Chir.* **180** 597-599, 1934. (c) Riegel, C., Ravdin, I. S., Morrison, P. J., and Potter, M. J. Studies of Gallbladder Function. XI The Composition of the Gallbladder Bile in Pregnancy, *J. A. M. A.* **105** 1343-1344 (Oct. 26) 1935. (d) Elman and Taussig.<sup>3a</sup> Fox,<sup>3b</sup> Antic and Goropevsek,<sup>4a</sup> Rosenbloom.<sup>4c</sup>

6 Mentzer.<sup>2</sup> Elman and Taussig.<sup>3a</sup> Antic and Goropevsek.<sup>4a</sup> Elton.<sup>11</sup> Schöndube and Kalk.<sup>1c</sup>

The quantities of cholesterol vary from less than 50 mg to 17.6 Gm per hundred cubic centimeters.<sup>7</sup> Various explanations are current as to the reasons for these variations and their significance in the theoretic considerations to which these data are applied.<sup>8</sup>

There are four distinct opinions as to the activity of the gallbladder in regard to biliary cholesterol: (1) that the gallbladder absorbs cholesterol from the bile,<sup>9</sup> (2) that it secretes cholesterol into the bile,<sup>10</sup> (3) that it simply concentrates biliary cholesterol *pari passu* with the

7 (a) Andrews, E. Detailed Studies of a Series of Gall-Bladder Cases, *Surg, Gynec & Obst* 57:36-50 (July) 1933. (b) Andrews, E., Hrdina, L., and Dostal, L. E. Etiology of Gallstones. II. Analysis of Duct Bile from Diseased Livers, *Arch Surg* 25:1081-1089 (Dec) 1932. (c) Fowweather, F. S., and Collinson, G. A. Certain Chemical Changes Associated with Gall-Stones, with Special Reference to the Relation Between Gall-Stones and Hypercholesterolaemia, *Brit J Surg* 14:583-608 (April) 1927. (d) Newman, C. E. Beitrag zum Studium der Gallenmiederschlags- und Gallensteinbildung, *Beitr z path Anat u z allg Path* 86:187-200, 1931. (e) Ravdin, I. S., Riegel, C., Johnston, C. G., and Morrison, P. J. Studies in Biliary Tract Disease, *J A M A* 103:1504-1509 (Nov 17) 1934. (f) Riegel, C., Ravdin, I. S., Johnston, C. G., and Morrison, P. J. Studies of Gall-Bladder Function. XIII. The Composition of the Gall-Bladder Bile and Calculi in Gall-Bladder Disease, *Surg, Gynec & Obst* 62:933-940 (May) 1936. (g) Elman and Taussig<sup>3a</sup> Fox<sup>3b</sup> Antic and Goropovsek<sup>4a</sup> Newman<sup>4d</sup> Rosenbloom<sup>4e</sup> Bockus and Eiman<sup>5a</sup> Riegel and others<sup>5c</sup>

8 Andrews, E., Schoenheimer, R., and Hrdina, L. Etiology of Gallstones. I. Chemical Factors and the Role of the Gallbladder, *Arch Surg* 25:796-810 (Oct) 1932. Fitz, R., and Aldrich, M. Clinical Observations on Certain Constituents of the Bile, *J A M A* 79:2129-2132 (Dec 23) 1922. Ivy, A. C. Physiology of the Gallbladder, *Physiol Rev* 14:1-102 (Jan) 1934. Riegel, C., Ravdin, I. S., and Rose, H. J. Studies of Gallbladder Function. XV. Cholesterol in Human Liver Bile, *J Clin Investigation* 16:67-72 (Jan) 1937. Whipple, G. H. The Origin and Significance of the Constituents of the Bile, *Physiol Rev* 2:440-459 (July) 1922. Elton<sup>4b</sup> Greene and others<sup>4c</sup> Newman<sup>4d</sup> Bockus and Eiman<sup>5a</sup> Bronner<sup>5b</sup> Andrews and others<sup>7b</sup> Ravdin and others<sup>7e</sup>

9 (a) Aschoff, L. Wie entstehen die reinen Cholesterinsteine? *München med Wchnschr* 60:1753-1756 (Aug 12) 1913. (b) Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, pp. 181 and 206. (c) Boyd, W. Gall-Bladder Problems, *Canad M A J* 12:689-693 (Oct) 1922. (d) Mentzer, S. H. Cholesterosis of the Gallbladder, *Am J Path* 1:383-388 (July) 1925. (e) Winklenwerder, W. L. A Study of Resorption from the Biliary Tract with Especial Reference to the Morphology and Permeability of the Cystic Epithelium, *Bull Johns Hopkins Hosp* 46:272-295, 1930. (f) A Study of the Lymphatics of the Gall-Bladder of the Cat, *ibid* 41:226-238, 1927. Antic and Goropovsek<sup>4a</sup>

10 Elman, R., and Graham, E. A. The Pathogenesis of the "Strawberry" Gallbladder, *Arch Surg* 24:14-22 (Jan) 1932. Naunyn, B. Die Gallensteine, ihre Entstehung und ihr Bau, *Mitt a d Grenzgeb d Med u Chr* 33:154, 1921. Elman and Taussig<sup>3a</sup> Ravdin and others<sup>7e</sup>

other biliary constituents,<sup>11</sup> and (4) that its activity varies with the relative concentration of cholesterol in the blood and bile<sup>12</sup>

#### METHODS

The bile was obtained as soon as possible at postmortem examination. Many cases proved unsuitable for study, since any number of conditions supervened, such as previous cholecystectomy, cholelithiasis with or without cholecystitis, hepatic atrophy, hepatic cirrhosis, jaundice of any type, limited examinations and so forth. In the satisfactory cases the intestines were removed first, and then the extrahepatic biliary tree was exposed. With as little disturbance to the gallbladder as possible, a hemostat was placed on the cystic duct and a second on the common hepatic duct. Then the liver and gallbladder were removed together.

The hepatic bile was aspirated from the hepatic ducts by a small syringe and a blunt needle of large caliber. Occasionally, apparently empty ducts can be made to yield a sufficient quantity by pressure on the substance of the liver. Care must be exercised to avoid contamination by gallbladder bile or blood. The bile of the normal-appearing gallbladder was then aspirated with a sharp needle of similar bore. The specimens were kept in the ice box until examined.

The chemical determinations were carried out in the following manner. As little as 0.2 cc of hepatic bile may prove sufficient for the determinations. The larger the quantity of bile obtained, the more accurate are the determinations. The bile is first diluted with distilled water in order to make a satisfactory bilirubin determination. One cubic centimeter of gallbladder bile is used and all the hepatic bile obtained. Dilution is carried out until the diluted bile is somewhat darker than a mildly icteric blood serum. All cellular debris or sediment in the 15 cc graduated test tubes used for collecting and measuring the bile is shaken until it is homogeneously suspended throughout. For bilirubin determinations the hepatic dilution may vary from five to thirty times and the cholecystic dilution from ten to one hundred and fifty times. One cubic centimeter of the diluted specimen is used for the bilirubin determination (according to the technic of Gibson and Goodrich<sup>13</sup>), which is recorded as milligrams per hundred cubic centimeters. In each instance the rest of the diluted hepatic bile is run for the cholesterol content according to the technic of Elman and Taussig<sup>14</sup>. For the determinations of gallbladder

11 Andrews, E., Dostal, L. E., Goff, M., and Hrdina, L. Mechanism of Cholesterol Gall-Stone Formation, *Ann Surg* **96** 615-623 (Oct.) 1932. Andrews, E., Dostal, L. E., and Hrdina, L. Etiology of Gallstones. IV. Is Cholesterol Excreted by the Gallbladder Mucosa? *Arch Surg* **26** 382-388 (March) 1933. Riegel, C., Johnston, C. G., and Ravdin, I. S. Studies on Gall Bladder Function. VIII. The Fate of Bile Pigment and Cholesterol in Hepatic Bile Subjected to Gall Bladder Activity, *J Exper Med* **56** 1-13 (July) 1932. Riegel, C., Ravdin, I. S., and Johnston, C. G. Studies of Gall-Bladder Function. VI. The Absorption of Bile Salts and Cholesterol from the Bile-Free Gall Bladder, *Am J Physiol* **99** 656-665 (Feb.) 1932. Fox<sup>3b</sup> Riegel and others<sup>2c</sup> Winkenwerder<sup>2f</sup>

12 Wilkie, A. L., and Doubilet, H. Passage of Cholesterol Through the Mucosa of the Gallbladder, *Arch. Surg* **26** 110-121 (Jan.) 1933.

13 Hawk, P. B. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1937.

14 Elman, R., and Taussig, J. B. The Quantitative Determination of Cholesterol in the Bile, *J Lab & Clin Med* **17** 274-279 (Dec.) 1931.

The total 1 cc of ten times diluted bile is used. The results are reported as milligrams per cubic centimeter.

The bilirubin determinations are done according to the technic of Gibson and Goodrich.<sup>15</sup> To 1 cc of diluted bile in a 15 cc graduated tube is added 1 cc of Ehrlich's diazo reagent, and the mixture is shaken. When the color is fully developed, 2 cc of saturated ammonium sulfate solution is added. Then 9 cc. of 95 per cent alcohol brings the solution to 13 cc., and the solution is shaken vigorously. The solution is made to the 15 cc mark with concentrated hydrochloric acid and stirred thoroughly. After five to ten minutes it is filtered and read against a pure bilirubin standard, previously prepared.

The unknowns to be used for the cholesterol determinations are mixed with 6 cc of 95 per cent alcohol. This is heated in a water bath to 70 C for a few minutes and filtered, which removes most of the bilirubin and protein. The resulting alcoholic solution is extracted three times with purified petroleum benzene U. S. P. (petroleum ether) in a separatory funnel, one uses in all about 100 cc. of purified petroleum benzene. This is evaporated to dryness on a water bath. The residue is taken up in chloroform, and the determination is made against a simultaneously determined standard solution.

#### RESULTS

The results obtained in the present investigation are summarized in the accompanying tables. Thirty-one cases were studied. These could be subdivided into three fairly definite groups: (1) cases in which the concentration of bilirubin and cholesterol was approximately equal—19 of the 31 cases (table 1), (2) cases in which the relative concentration of the bilirubin was greater than that of cholesterol, indicating absorption of cholesterol—8 cases (table 2), and (3) cases in which the relative concentration of the cholesterol was greater than that of bilirubin—4 cases (table 3).

With the exception of the report of Elman and Taussig<sup>2a</sup> no other paper presents such data as these simultaneous determinations of hepatic and gallbladder cholesterol and bilirubin.

Wide variations in the bilirubin and cholesterol content in both hepatic and gallbladder bile existed in all three groups. In group 1 (table 1) the extreme variations for the hepatic bilirubin were 96 to 1,720 mg per hundred cubic centimeters and for the gallbladder bilirubin were 96 to 6,000 mg per hundred cubic centimeters. The ratios of concentration of the hepatic bilirubin varied from 0.96 to 24.5. The value for hepatic cholesterol was as low as 0.25 mg and as high as 7.81 mg per cubic centimeter. The cholesterol content per cubic centimeter of bile from the gallbladder was from 0.8 mg to 17.85 mg. The ratio of cholesterol in the gallbladder bile to cholesterol in the liver bile varied from 0.6 to 21.4.

<sup>15</sup> Gibson and Goodrich<sup>15</sup> used 2 cc of serum. Therefore, these results are multiplied by 2 to get results in milligrams per hundred cubic centimeters.



TABLE 1—Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects Cases in Which the Concentration of Bilirubin and That of Cholesterol Was Approximately Equal

Em balm	Age, Years	Sex	Hepatic Bilirubin, Mg per 100 Cc	Gall bladder Bilirubin, Mg per 100 Cc	Ratio of Gall bladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol, Mg per Cc	Gall bladder Cholesterol, Mg per Cc	Ratio of Gall bladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver, Gallbladder, Bile Ducts)
—	42	F	912	1 560	1.7	1.5	3.33	2.2	Malignant glioma bronchopneumonia	
+	29	M	230	3,540	15.4	0.5	7.5	15.0	Malignant glioma bronchopneumonia	Gallbladder cholesterol polyps
+	50	M	200	4,905	24.5	0.25	5.36	21.4	Carcinoma of lung cerebral metastasis	
+	63	M	1,720	2 520	1.5	7.81	9.09	1.2	Nephrolithiasis pyelonephritis icterus grade 2* bronchopneumonia	Gallbladder cholesterosis grade 2*
+	67	M	523	1 095	3.8	3.31	12.0	3.6	Chronic duodenal ulcer broncho- pneumonia	Liver atrophy grade 1+*
—	52	F	540	1,540	2.9	2.47	12.0	4.0	Calcareous aortic stenosis dilatation of left ventricle	Cysts of liver
—	48	F	512	1 570	3.1	3.6	13.34	3.7	Exophthalmic goiter hemor- rhage	Gallbladder cholesterosis grade 2*
+	30	F	160	180	1.2	3.64	6.0	1.6	Aneurysm of circle of Willis rupture with hemorrhage	
+	38	M	112	547.5	4.9	2.22	9.0	4.1	Carcinoma of larynx, broncho- pneumonia	Gallbladder cholelithiasis cholesterol polyps
+	41	M	504	2 628	5.2	6.57	17.85	2.7	Adenomatous goiter broncho- pneumonia	Liver subcapsular lipoma
—	33	F	1 038	6 000	5.8	1.16	10.0	8.6	Nephrectomy for tuberculosis pul- monary edema with beginning pneumonia	Cystic duct joined right hepatic duct
+	65	M	96	286	3.0	0.74	3.34	4.5	Appendectomy for gangrene perit- onitis pulmo- nary embolism	Gallbladder numerous cholesterol polyps
—	77	M	240	410	1.7	3.0	7.5	2.5	Aneurysm ab- dominal aorta, hemorrhage	Liver few scattered hyaline tubercles
—	93	F	115.2	159	1.4	0.45	0.8	1.8	Erysipelas of face	Gallbladder 6 black stones
—	54	M	510	5 700	11.2	0.625	8.33	13.3	Carcinoma of sigmoid flexure pelvic peritonitis bronchopneu- monia	Gallbladder cholesterol polyps cho- lesterosis grade 2*
—	71	M	670	1 320	2.0	1.25	2.14	1.7	Gastrojejunal ulcer broncho- pneumonia	Gallbladder cholesterol is grade 1*
—	63	M	840	2,363	2.8	1.876	5.555	3.0	Cerebral arterio- sclerosis grade 4 bilateral broncho- pneumonia	
—	81	M	100	96	0.96	1.575	1.0	0.6	Bronchopneu- monia	Gallbladder cholesterol stone muco- sal scarring cholesterol's grade 1
—	64	M	1 215	4 760	3.5	1.023	4.2	4.1	Carcinoma of colon intestinal obstruction	Gallbladder cholesterol polyp liver multiple metastases

\* On a basis of 1 to 4

A similar variation in all aspects was found in the cases in group 2, which are classified together on the basis of a higher bilirubin concentration than cholesterol concentration (table 2). In these 8 cases the concentration of bilirubin in the hepatic bile varied from 112 to 1,572

TABLE 2—Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects Cases in Which the Concentration of Bilirubin Was Greater Than That of Cholesterol

Initial	Age, Years	Sex	Hepatic Bilirubin, Mg per 100 Cc	Gall bladder Bilirubin, Mg per 100 Cc	Ratio of Gall bladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol, Mg per Cc	Gall bladder Cholesterol, Mg per Cc	Ratio of Gall bladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver, Gallbladder, Bile Ducts)
+	55	F	218	2,920	11.8	2.14	13.64	6.4	Rheumatic heart disease, dilatation of left ventricle	Liver congestion with atrophy, grade 2*
+	50	M	112	1,950	17.7	2.22	10.0	4.5	Carcinoma of stomach, bronchopneumonia	
—	60	M	1,572	3,836	2.4	13.3	12.36	0.9	Aneurysm of aorta, rupture with hemorrhage	
+	32	M	292	1,424	4.9	3.33	6.25	1.9	Lindau's disease, internal hydrocephalus, grade 2+*	Liver small cyst left lobe, gallbladder many small cholesterol polyps, cholesterosis, grade 1*
+	32	M	350	2,880	8.2	1.85	6.8	3.7	Acute purulent cerebrospinal meningitis	Gallbladder cholesterol polyps, numerous small stones
+	18	F	320	1,260	3.9	5.35	6.82	1.3	Abscess left temporoparietal region	
—	31	M	200	1,650	8.25	1.17	2.63	2.3	Tuberculosis (pulmonary and osseous), bronchopneumonia	
—	66	M	240	1,495	6.2	4.28	9.375	2.2	Spongioblastoma, hemorrhagic edema of lungs	

\* On a basis of 1 to 4

mg per hundred cubic centimeters and in the gallbladder bile from 1,260 to 3,836 mg per hundred cubic centimeters. The ratio of bilirubin concentration by the gallbladder varied from 2.4 to 17.7. The concentration of cholesterol varied from 1.17 to 13.3 mg per cubic centimeter in the hepatic bile and from 2.68 to 13.64 mg per cubic centimeter in the bile from the gallbladder. The ratio of cholesterol concentration was from 0.9 to 6.4.

Group 3 (table 3), in which the cholesterol concentration was higher than the bilirubin concentration, showed unusually high values for hepatic bilirubin. In these 4 cases, this value varied from 240 to 1,200 mg per hundred cubic centimeters. The value for bilirubin in the gallbladder was likewise high. The lowest figure was 1,080 mg, and the highest, 2,040 mg, per hundred cubic centimeters. The ratio between the amount of gallbladder bilirubin and hepatic bilirubin varied between 1.6 and 6.2. The cholesterol values were from 0.416 to 4.26 mg per cubic centimeter for the hepatic bile and from 4.5 to 17.18 mg per cubic

TABLE 3—Comparative Concentration of Hepatic Bilirubin and Cholesterol by the Gallbladder in White Subjects Cases in Which the Concentration of Cholesterol Was Greater Than That of Bilirubin

Em balled	Age Years	Sex	Hepatic Bilirubin Mg per 100 Cc.	Gall bladder Bilirubin Mg per 100 Cc.	Ratio of Gall bladder Bilirubin to Hepatic Bilirubin	Hepatic Cholesterol Mg per Cc.	Gall bladder Cholesterol Mg per Cc.	Ratio of Gall bladder Cholesterol to Hepatic Cholesterol	Cause of Death	Gross Pathologic Change (Liver Gallbladder Bile Ducts*)
+	53	F	393.3	1 080	2.7	1.5	10.0	6.7	Carcinoma of colon pulmo- nary embolism	
+	57	M	392.0	2 040	5.2	0.416	10.0	30.1	Carcinoma of rectum general ized peritonitis	Liver echinococcus cyst (?)
—	42	F	1 200.0	1 900	1.6	4.26	17.18	4.0	Abscess of brain increased intra cranial pressure	
—	60	F	240.0	1 500	6.2	0.41	4.5	11.0	Carcinoma of colon intestinal obstruction	Gallbladder cholesterosis grade 1*

\* On a basis of 1 to 4

centimeter for the bile from the gallbladder. The ratio of cholesterol in the gallbladder bile to cholesterol in the hepatic bile fell between 4 and 36.1.

It may be seen in these three tables that the actual figures for each group are not so different from those of the others. They are differentiated by the fact that the two constituents studied are concentrated unequally in groups 2 and 3 and equally in group 1.

Simply as a matter of record, these figures may be added to the quantitative study of biliary physiology. They show that the hepatic bile may contain as little bilirubin as 96 mg or as much as 1,720 mg per hundred cubic centimeters. The gallbladder bilirubin may vary from 96 to 6,000 mg per hundred cubic centimeters. The concentration of cholesterol may be from 0.25 to 13.3 mg per cubic centimeter in the

hepatic bile and from 0.8 to 17.85 mg per cubic centimeter in the gallbladder. The extreme variations in the hepatic bile point to great flexibility in the excreting power of the liver.

Similarly, the wide variation both in the actual figures for cholecystic bilirubin and amounts of cholesterol and in the ratios of concentration of bilirubin and cholesterol by the gallbladder speaks of a remarkable flexibility in function of the gallbladder.

#### COMMENT

These figures have their primary significance in adding to the quantitative studies of bilirubin and cholesterol determinations with more recent methods. They confirm previous studies in their wide range of value.

Secondarily, by having studied the bile from the liver and from the gallbladder simultaneously, we may correlate the quantities present and infer from these ratios something as to gallbladder function. It may be seen from the numbers of cases in each table that the preponderance of evidence is in favor of simple concentration of cholesterol by the gallbladder. Next, the evidence would favor the hypothesis that cholesterol is absorbed by the mucosa of the gallbladder.

Since only 4 of the cases fell into the group with higher concentrations of cholesterol, that is, indicating secretion of cholesterol by the gallbladder, it might be inferred that these instances are rare. However, the fact that there are cases which fall into all three groups is evidence for the contention of Wilkie and Doubilet<sup>12</sup> that the direction of the passage of cholesterol across the mucosa of the gallbladder depends on the relative concentration of this substance in the bile and in the blood.

The most profound objection to a study of this nature is that it is determining physiologic data on postmortem material. Agonal and postmortem changes might profoundly influence the bile secreted by the liver or the bile already present in the gallbladder. As regards the latter possibility, Elman and Taussig<sup>13</sup> maintained that after death the mucosa of the gallbladder desquamates rapidly and that high values are partly due to cellular debris. Doyon and Dufort<sup>16</sup> agreed with this statement. There is evidence from these sources that cellular desquamation may lead to increased cholesterol in the bile. Note, however, that in not one of these 4 cases was there marked cholesterosis, nor were cholesterol polyps present. Grossly, the conditions were comparable to those of the other two series.

16 Doyon, M., and Dufort, M. Contribution à l'étude de la sécrétion biliaire élimination de la cholestérine par la bile, *Arch de physiol norm et path* 8: 57-59, 1896.

Elton<sup>4b</sup> compared postoperative and postmortem bile and found that "The possible influence of dehydration, age, cause of death, and interval between death and necropsy were not demonstrable, and furthermore, gallbladder bile apparently undergoes a most excellent state of preservation in the intact viscus for at least forty-eight hours" He stated further, "No correlation between bile concentration and therapy or preagonal abstinence from food in prolonged illnesses could be determined"

As regards the possible agonal changes in cholesterol metabolism, Goff, Hrdina and Andrews<sup>17</sup> studied two series of dogs, in one of which the animals were killed and in the other of which they died, after ligation of the common duct In the two series the average cholesterol content of the bile was the same, but in the dogs that died the bile salt content was 25 per cent lower This study would indicate that there is no agonal change in hepatic secretion of cholesterol

The contention that hepatic bile is not of constant composition and that the bile stored and concentrated by the gallbladder may originally have been of different composition from the hepatic bile studied post mortem seems unanswerable and is a formidable obstacle in drawing satisfactory conclusions from this study

That the gallbladder is ideal anatomically for concentrating fluids is universally recognized The degree to which it may concentrate is debated Schondube and Kalk<sup>4c</sup> expressed the opinion that it can concentrate bilirubin one hundred times, Newman,<sup>4d</sup> only five to forty times—an average of about twenty times In dogs, Rous and McMaster<sup>18</sup> found a concentration factor of ten times for bilirubin According to the figures in the present study, bilirubin concentration may reach twenty-four and one-half times the hepatic value in the gallbladder The highest ratio for cholesterol was thirty-six and one-tenth times If one uses the lowest figure obtained for hepatic bilirubin (ninety-six) and the highest for gallbladder bilirubin (six thousand), one may infer that under extreme conditions bilirubin might be concentrated as high as sixty times in the gallbladder

#### SUMMARY

The present investigation demonstrates that sufficient bile can be removed post mortem from the extrahepatic biliary tree for a comparative study of hepatic and gallbladder bile It adds a new group of quantitative determinations for both bilirubin and cholesterol from the gallbladder

17 Goff, M., Hrdina, L., and Andrews, E. Effect of Prolonged Stasis on the Bile Salt-Cholesterol Ratio, *Proc Soc Exper Biol & Med* 29 549-550 (Feb) 1932

18 Rous, P., and McMaster, P. D. The Concentrating Activity of the Gall Bladder, *J Exper Med* 34 47-75 (July) 1921

and common hepatic duct. It shows that there is a marked variation in these substances in the liver bile and in the concentrated gallbladder bile.

Comparative studies of the relative concentration of bilirubin and cholesterol by the gallbladder indicate that in the majority of instances (19 of 31) the cholesterol of the hepatic bile is simply concentrated *pari passu* with the concentration of bilirubin. However, 12 of the 31 cases studied do not fit in with this hypothesis, and evidence is given that in certain instances cholesterol may be either added to or removed from the gallbladder, as Wilkie and Doubilet<sup>12</sup> postulated.

## REVIEW OF UROLOGIC SURGERY

ALBERT J SCHOLL, M D  
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SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M D  
BUDAPEST, HUNGARY

ALEXANDER B HEPLER, M D  
SEATTLE

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NEW YORK

GERSHOM J THOMPSON, M D  
AND

JAMES T PRIESTLEY, M D  
ROCHESTER, MINN

EGON WILDBOLZ, M D  
BERNE, SWITZERLAND

AND  
VINCENT J O'CONOR, M D  
CHICAGO

(Concluded from page 1304)

### BLADDER

*Hunner's Ulcer*—Rusche and Hager <sup>48</sup> presented some observations on the development of malignancy in Hunner's ulcer, and they reported 2 cases

In 1 case the patient was a man aged 26 years, in whom definite Hunner's ulcer was found. Treatment consisted of the usual measures. Fifteen years later he was again examined. He was in a critical condition at this time and died shortly afterward. Cystoscopic examination had not been made. Microscopic examination of the wall of the bladder showed a definite carcinoma. The tumor was anaplastic, and a growth infiltrated the tissues. It resembled a scirrhus neoplasm, such as might have been found in the presence of gastric carcinoma.

In the second case the patient was a woman 65 years old who was seen in 1933, at which time several irregular portions 1 cm in diameter had been seen in the posterior wall of the bladder during cystoscopic

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<sup>48</sup> Rusche, C, and Hager, B H. Further Observations on the Development of Malignancy in Hunner Ulcer. *Tr Am A Genito Urin Surgeons* **32** 203 210 1939

examination. These portions were typical of interstitial cystitis. This patient was seen again three years later, at which time an extensive infiltrating neoplasm involving most of the surface of the bladder was found.

Of interest is the fact that there was no demonstrable evidence of metastasis in either case, in each the neoplasm seemed to be limited to the interior of the bladder.

Hagner,<sup>49</sup> in discussing Rusche and Hager's article on Hunner's ulcer, stated that he had reported on a woman whom he had had under observation for nearly three years. She was suffering from Hunner's ulcer. She had been at one time practically free from symptoms, and he had not seen her for about six months. She returned and said that she had experienced some amount of bleeding. A cystoscopic examination was made, and unquestionably there was a carcinoma, about the size of a thumbnail, situated at the top of her bladder. The patient died about six months later from general abdominal metastasis of the primary lesion.

Hagner stated that it used to be a great comfort to him to tell patients who had a solitary ulcer that such an ulcer practically never heals but that it never develops into a neoplasm. This statement cannot be made now. Hunner had reported only 1 case of such a transformation at the time Hagner reported his case, and, as far as Hagner knew, his case and Hunner's are the only 2 reported cases in which Hunner's ulcer has developed into a malignant neoplasm.

Sisk<sup>50</sup> pointed out the fact that sulfanilamide will benefit many patients who have old chronic Hunner's ulcer. He discussed the condition of 2 patients. One of these had been treated elsewhere for about five years and had been under Sisk's observation for about seven years. By means of sulfanilamide therapy she was almost entirely relieved of her symptoms and had remained so for a year at the time of Sisk's report. Another patient, who had a lesion of seven or eight years' standing, had been entirely free of pain for more than a year at the time Sisk spoke of her, although she still had frequency of micturition, urinating about once every two to three hours.

*Tumor*—Colby<sup>51</sup> stated that evidence collected thus far gives little support to the contention that malignant tumors of the bladder can be cured by supervoltage irradiation. The method is recent, and the dosage

49 Hagner, F. R., in discussion on papers of Rusche and Hager and Sisk and Neu, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 212, 1939.

50 Sisk, I. R., in discussion on papers of Rusche and Hager and Sisk and Neu, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 212, 1939.

51 Colby, F. H., *Supervoltage Radiation in the Treatment of Bladder Tumor*, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 225-231, 1939.



is still undetermined. In Colby's cases, the cancer seems to have been affected to a greater extent by supervoltage treatment than by other forms of external irradiation. Extensive tumors have regressed to the point of gross disappearance, but there is evidence that even in such a favorable event cancerous cells persist in the deep layers of the wall of the bladder. Although the intravesical portions of a tumor may disappear, it has been evident that large regions of cancerous tissue can persist in the deep structures, so that cancer will reappear in the bladder. Recurrent growths have responded less well to additional irradiation, and in no instance has the tumor disappeared again after more treatment. The most favorable responses were obtained with patients who had received no previous treatment. Colby's experience during the two years prior to his report caused him to feel that this treatment should be used only for patients who have advanced tumors or for old and debilitated patients and that any tumor of the bladder suitable for surgical treatment should be operated on.

Gayet<sup>52</sup> stated that leiomyosarcoma of the bladder is a form of tumor that has not been sufficiently brought to the attention of urologists. It is more common than is classically believed, has a rapid course and terminates fatally in four to six months after its clinical recognition. In addition to the symptoms that usually accompany cancer of the bladder, intense fetid and necrotic cystitis is present. The appearance of the lesion at the outset, when it is discovered, is that of a pedunculated and regular tumor, in contrast to the fulminating evolution which is the general characteristic of vesical tumors. Such pedunculation and regularity constitute a ready source of error in diagnosis.

Gayet observed within a few months 3 patients who had tumors of this kind. He presented the histories of these patients. Study of the literature reveals that leiomyosarcomas of the bladder are more common among men than among women and that, unlike most sarcomas, which attack the young, they have been observed to afflict patients who are mostly between the ages of 40 and 60 years, an observation which suggests that they possibly develop on the basis of a preexisting myoma. Some of them may be envisaged as the possible result of degeneration of a benign vesical tumor. Unquestionably, purely myomatous portions coexist with other portions that exhibit malignant degeneration. It is unfortunate that no case of benign leiomyoma has been published in which the transformation into sarcoma has actually been observed secondarily, although 1 of Gayet's cases suggests this eventuality.

The fundamental anatomic appearance of such a neoplasm reveals both of its constituents, muscular hypertrophy and degeneration of con-

52 Gayet, R. Les leiomyo-sarcomes de la vessie, *J d'uro*l 48 320 333 1940

nective tissue. Three sites of election have been observed, as is the case when uterine myomas are present (1) interstitial and extraparietal, (2) submucous, or cavitory, and (3) peripheral, or excentric. The point of implantation is most frequently the trigon, but the tumors have been found in the lateral walls and even in the dome of the bladder. The size and weight of these tumors are very variable, weights of 500 Gm and 5 pounds (1.3 Kg) having been reported. In 2 of Gayet's cases the entire bladder was invaded. The tumor may be pedunculated or sessile, or several pedicles may be twisted about a common axis. Necrosis is rapid because of deficient nutrition. Infection appears, which is carried rapidly to the kidneys. Nearby organs are seldom invaded, only 1 instance of metastasis (to the humerus) having been observed in 15 cases collected by Kretschmer.

Microscopically, leiomyosarcoma is characterized by cellular anarchy, the considerable size of each element and the presence of numerous mitoses, confirming the malignancy of the tumor. Clinically, the first signs are pollakiuria and sometimes marked dysuria, followed by capricious hematuria which appears on every attempt by the surgeon at exploration. In diagnosis, the most important signs are (1) the fetid urine filled with debris and (2) the cystoscopic appearance, which is clearly that of cancer when the mass is of the type of an infiltrated tumor (when, however, it is rounded and regular, resembling a myoma, error is more likely to occur). Only biopsy insures a certain diagnosis, revealing an association of hypertrophied muscle fibers and sarcomatous cells.

Many urologists regard such a condition as too hopeless for treatment. Others have tried the various form of irradiation and surgical treatment, none of which, however, have proved to be more than palliative. Cystostomy, although it permits partial evacuation of urine and debris, often causes exacerbation instead of relief of pains, it also hastens the spread of the malignant neoplasm. Cystectomy, whether total or partial, fails. It has been followed by rapid recidivation and death in all the author's cases. The extreme malignancy of these tumors does not encourage the surgeon to attempt their removal.

*Exstrophy*—Godard<sup>53</sup> applied a form of technic somewhat different from the usual approach in 2 cases of exstrophy of the bladder and in 1 of epispadias. Having observed the difficulty involved in closing the bladder if care is not taken to mobilize it widely and to bring it down as low as possible in the pelvis, he decided on prerectal pelvic transposition of the bladder. The method is not applicable to female patients, because of the anatomic position of the bladder in females, and should

53 Godard, H. L'exstrophie vésicale et l'épispadias masculine, leur traitement par la transposition pelvienne pré-rectale de la vessie, *J. d'urolog.* 47 97-109 (Feb) 1939

not be tried in boys until they are 5 or 6 years of age, because of the narrowness of the bony pelvis in such patients

The technic has two principal aims (1) invagination of the bladder and its reconstitution as a reservoir for the urine and (2) reposition of the bladder within the pelvis, with a view either to its control by the anal sphincter or to later reconstruction of the urinary passages to a nearly normal state by Marion's plastic transfixing operation

The genital system (penis and prostate gland) is left in place in the pubic region, the urinary system having become pelvic (analogous to an embryonic cloaca), or being drained temporarily by way of the perineum until such time as urethroplasty is done. The technic is briefly as follows

In the first stage the patient is placed in the horizontal position, and two ureteral catheters are used to drain the urine from the operative field, while the bladder is kept invaginated by a pack of compresses. After a traction thread of silk has been placed around the neck of the bladder, a racket-form incision is made, it passes as nearly as possible to the bottom of the urethrovesical furrow, which often can be recognized behind the verumontanum. In the second stage the globe of the bladder is freed, and the peritoneum is cautiously separated from its postero-superior surface. In front this dissection is rather laborious, for here and there is a vascular pedicle that must be tied. The dissection proceeds downward, forward and slightly to the side without any difficulty. The bladder is then progressively sunk down into the pelvis, where the silk thread will at once permit fixation of it.

After incision of the skin at the anterior margin of the anus, the outermost fibers of the anal sphincter are split, a wide band of internal sphincter being left intact. In carrying out the dissection the pelvis is entered, and the vesical silk traction threads are picked up.

This stage is somewhat difficult, since traction has to be made not only on the vesical orifice but on the catheters, a competent assistant is required to keep an eye on the abdominal part of the operative field and to facilitate the maneuvers. The vesical tamponade is removed, care being taken to maintain in place the ureteral sounds, which are left in position for several days or, better, are replaced by a Pezzer catheter, firmly fixed.

The operation ends with partial closure of the abdominal incision, partial closure frequently being all that can be done, because of lack of available skin and muscle for complete closure. Drains are placed in the incision, and gauze is inserted to fill up the dead spaces.

After what is usually a long process of cicatrization, the new orifice appears in front of the anus, from which it is separated by a sort of spur resembling a swollen hemorrhoid.

Four patients have been treated by this method, and the procedure has been followed later by operation for epispadias. Esthetic results have been excellent, and the degree of continence obtained, although not perfect, has been remarkable. The technic can and should be further improved. Since children born with these deformities commonly exhibit mental deficiency as well, it is hardly likely that any of them can ever urinate normally.

*Diverticula*—Radical complete diverticulectomy is often a difficult and dangerous procedure. Barnes<sup>54</sup> described a technic for the successful obliteration of large vesical diverticula which cause residual urinary and vesical symptoms. This procedure utilizes a combination of the intravesical and extravesical approaches and provides adequate exposure of the interior of the diverticulum, so that the mucosa can be removed by stripping or by cauterization. The diverticular orifice and the incisions through the wall of the bladder are sutured with no. 000 chromic catgut in two layers, a muscular and a submucosal layer, and the diverticular cavity is treated with an antiseptic solution and drained extravesically. Shock and postoperative perivesical sepsis are reduced to a minimum by this technic, and there has been no persistence or recurrence of the diverticulum.

Thompson, Kermott and Cabot<sup>55</sup> pointed out the fact that diverticula contain all the coats of the bladder and are truly congenital in origin but become symptomatic later in life because of obstruction of the vesical neck. Various plans of treatment have been devised, such as (1) two stage suprapubic prostatectomy and diverticulectomy, either in the order given or in reverse order, (2) a one stage operation, and (3) transurethral prostatic resection with or without subsequent diverticulectomy.

These authors studied 14 patients who had vesical diverticula and who were treated only by means of suprapubic prostatectomy. None at the end of a two year follow-up study needed diverticulectomy, yet most had had a long and complicated convalescence. Secondary diverticulectomy is a much more serious operation in such cases than the primary operation for diverticulum would have been.

Ninety-six patients who had vesical diverticula and who were treated by transurethral resection also were reported on. The diverticula varied in size from small (24 cases) to large, that is, equivalent in size to the bladder (17 cases). The postoperative course was short, smooth and uncomplicated. All the patients were almost completely relieved of

54 Barnes, R. W. Surgical Treatment of Large Vesical Diverticula. Presentation of a New Technique, *J. Urol.* **42** 794-814 (Nov.) 1939.

55 Thompson, G. J., Kermott, L. H., and Cabot, H. The Management of Diverticulum of the Bladder. Ninety-Six Patients Treated by Transurethral Prostatic Resection, *Surg., Gynec. & Obst.* **70** 115-119 (Jan.) 1940.

their symptoms by the surgical treatment. Subsequent diverticulectomy has not been necessary, but if it should be necessary, it ought to be a comparatively simple primary procedure. Diverticulectomy now is done only a third as many times at the Mayo Clinic as formerly, a fact which tends to demonstrate the satisfactory results which can be obtained from transurethral resection. Of follow-up study the 96 patients mentioned revealed that they enjoyed satisfactory results as to both symptoms and amount of residual urine present.

Diverticulectomy is indicated (1) when the diverticulum does not drain adequately through a small orifice, (2) for young men, who have poor drainage after resection, (3) when stone or carcinoma is present in the diverticulum, and (4) when ureteral obstruction is present.

*Regeneration*—Sisk and Neu<sup>56</sup> reported a case of regeneration of the bladder. The patient was a man 56 years old. At operation a large carcinoma was found to extend across the dome of the bladder. Since this portion of the tumor had not invaded the perivesical tissues, the operation was continued in the hope that it might be possible to resect the tumor. The peritoneum having been dissected free, the bladder was opened behind the region involved by the tumor. As exploration of the bladder proceeded, it was found that the tumor completely encircled the neck of the bladder. The entire bladder was removed with the exception of a small portion of the posterior wall, which measured about 3 by 3 cm. The ureters were cut across, and, since it was found that the tumor had invaded to some extent the right lobe of the prostate gland, a number of radium emanation seeds were introduced into this region. When the operation had progressed to this point, the patient exhibited definite evidence of shock. Drains were introduced into the bed from which the bladder had been removed, and the incision was closed in layers. The patient was seen four months later. Shortly after returning for consultation he began to void urine through the urethra. The incision had healed completely. He was at this time voiding about every two hours. The suprapubic incision was well healed. A cystogram permitted the introduction of 3 to 4 fluidounces (88 to 118 cc) of medium. The fundus of the bladder appeared to be smooth and regular in outline. The patient died some months later.

Sisk and Neu stated that in spite of the fact that permission to do necropsy was not obtained and that there was no definite knowledge of the actual degree of regeneration of the bladder, it was clear that within about two and a half months after removal of all except a small segment of the posterior wall of the bladder a cavity developed which solved the problem wholly and suitably.

<sup>56</sup> Sisk, I R, and Neu, V F. Regeneration of the Bladder. Report of a Case, *Tr Am A Genito-Urin Surgeons* 32: 197-202, 1939.

*Neurogenic Disease of the Bladder*—Nesbit and Gordon<sup>57</sup> stated that uninhibited neurogenic disease of the bladder is a clinical syndrome characterized by frequency of urination, nocturia and imperative micturition. The causative lesion is situated in the central nervous system and not in the lower part of the urinary tract. Differential diagnosis must be made to distinguish uninhibited neurogenic disease of the bladder from irritative lesions of the urinary tract, such as infection and early prostatism. Drug therapy is the only available form of treatment at present. The drug of choice is tincture of belladonna. Beneficial results were obtained in 9 of 16 cases in which the patients were treated with this drug. Twenty-five cases were reported in detail.

*Cystitis Associated with Osteomyelitis*—Mathé<sup>58</sup> reported 3 cases of long-standing intractable cystitis secondary to chronic osteomyelitis of the pubic bone, a late complication of fracture of the pelvis and rupture of the bladder. In all 3 cases the patients were relieved by operation.

Three types of chronic cystitis are observed: (1) that resulting from traumatic rupture of the bladder, associated with fracture of the pelvis or luxation of the pelvic bones, (2) that caused by osteomyelitis of the symphysis and ramus of the pubis occurring after operations on the bladder or by osteomyelitis of the pelvic girdle following operations on its component bones, and (3) cystitis referable to nontuberculous hematogenous osteomyelitis of the pubis and thigh, which usually occurs during childhood.

Chronic urinary infection associated with hematogenous and traumatic osteomyelitis of the pelvic girdle is the result of complicating infected sequestrums, involucrums, abscesses, spontaneous rupture of the bladder and osteovesical fistulas.

The condition should be suspected when patients present chronic pyuria with which there is a history of previous fracture of the pelvis or of attacks of osteomyelitis during childhood. Rectal and vaginal palpation enables the examiner to detect distended portions in the bones making up the pubic arch, such distention is referable to sequestrums, abscesses and fistulous tracts. Cystoscopic examination enables the urologist to visualize migratory fragments of bone and sequestrums, associated stones and the openings of fistulous tracts. Roentgen examination of the pelvic girdle demonstrates regions of rarefaction and fraying.

57 Nesbit, R. M., and Gordon, W. G. The Uninhibited Neurogenic Bladder: A Clinical Syndrome with Report of Twenty-Five Cases, *Tr. Am. A. Genito-Urin. Surgeons* 32: 213-224, 1939.

58 Mathe, C. P. Management of Intractable Cystitis Associated with Vaginal Fistula and Osteomyelitis of Pelvic Girdle. Report of Three Cases Following Traumatic Rupture of the Bladder and Fractured Pelvis, *J. Urol.* 43: 543-549 (April) 1940.

of bone margins caused by osteomyelitis and periostitis. Cystograms show distortion of the bladder and displacement as well as communicating osteovesical fistulas.

Prophylactic treatment consists of hermetic diversion of the urinary stream by suture of the wall of the bladder to the skin at the time of original surgical intervention for rupture of the bladder. Surgical treatment consists of sequestrectomy, curettage of infected bone, debridement of infected surrounding tissues, removal of connecting fistulous tracts and drainage of contiguous abscesses in conjunction with cystotomy or drainage by catheter.

*Incontinence*—Influenced by the excellent results obtained by Cathelin in the treatment of idiopathic and infantile incontinence of the urinary bladder by epidural injections of solution of sodium chloride, Marti<sup>59</sup> tried this method of treatment for incontinence caused by insufficient control of the sphincter. He injected 20 to 30 cc of a 2 per cent solution of sodium chloride into the sacral canal at weekly intervals. He never made more than six injections, and it was never necessary to hospitalize a patient. Marti tried this method in 17 cases, in 16 of which he obtained satisfactory results.

*Fistula*—O'Connor<sup>60</sup> reported on 4 patients who had vesicovaginal fistulas who were cured by cystoscopic and vaginal electrocoagulation after attempts at surgical repair had failed.

Healing is aided by the insertion of an indwelling urethral catheter and placement of the patient in a posture which is suitable for keeping the fistulous region as dry as possible. The hydrogen ion concentration of the urine should be kept at 5.5 or less by the use of the acid ash diet and ammonium nitrate to prevent incrustation of the coagulated tissue and deposition of lime in the catheter.

This method is not indicated in the treatment of fistulas involving the floor of the bladder or in cases in which there are extensive defects in tissue but should receive more consideration than it has received in the past, especially when unsuccessful surgical repair has resulted in formation of a small lateral opening.

*Contracture of Vesical Neck*—Thevenard<sup>61</sup> discussed the clinical picture and treatment of diseases of the neck of the bladder in women. The principal signs are those of obstruction to the outflow of urine, which causes first progressive dysuria, then pollakiuria and, if retention is of high degree, a sensation of weight in the hypogastrium. Simul-

59 Marti, T. Zur Behandlung der durch ungenügenden Sphinkterschluss bedingten Harninkontinenz der Frauen, *Ztschr f Urol* **33** 692 696, 1939.

60 O'Connor, V. J. Non-Surgical Closure of Vesicovaginal Fistula, *Surg., Gynec & Obst.* **70** 826 827 (April) 1940.

61 Thevenard, P. La maladie du col vesical chez la femme, *J d'urcol* **48** 296 319, 1940.

Simultaneously, the usual signs of intoxication appear, chief among which is uremia, indicating repercussion on the renal function, finally, there is dilatation of the pelvis and ureters, with bilateral hydronephrosis, which grows constantly worse until incontinence appears as the last stage of the condition. Not all these signs are necessarily present in any given case. Other conditions which appear are congestion, spasm and infections, among these the most frequent is cystitis, which causes a burning sensation and frequency of urination. What are at first temporary attacks tend to become permanent, they may lead to bleeding of the vesical mucosa and then to bullous edema and the appearance of inflammatory new growths. As these progress, the capacity of the bladder shrinks. Dynamic disturbances set up by the infection aid in the development of ureteropyelitis and pyelonephritis of varying acuteness. Two special complications may then develop, namely, diverticulum of the bladder and vesical lithiasis.

In diagnosis, the chief points to consider are the history of the patient and the results of cystoscopic examination. An early and constant indirect sign is the existence of columnar formation, an occurrence which attests to the struggle of the vesical muscles against the obstruction at the neck of the bladder. Less constant are such signs as modification of the neck of the bladder evidenced by thickening of the sphincter, irregularity of the orifice and various deformations. Urethroscopic examination, however, shows nothing that can be called absolutely characteristic.

The only form of radical treatment is resection of the neck of the bladder, which may be carried out by the high transvesical method, with scissors (Marion's method), or transurethrally by high frequency current. The first procedure is now seldom used, being suitable only in exceptional cases in which endoscopic resection has failed or when cystostomy is required for other, concomitant conditions.

The type of instrument chosen for application of high frequency current may be any one of those in common use for endoscopic prostatic resection, and the instrument is of less importance than the surgeon's judgment of just how much tissue to resect. The danger of production of incontinence, which was real in the past, now practically does not exist in the hands of an experienced urologic surgeon. In an occasional case temporary incontinence may occur and may last a few weeks or months, but it almost invariably disappears with the passage of time. The best approach to the neck of the bladder appears to be the circumferential route, which requires the least penetration for removal of a given amount of tissue. This mode of approach smooths out all irregularities and leaves the vesical neck perfectly circular, often the procedure can be accomplished at a single operation, after which a rubber catheter is inserted, left in place for from two to four days and



removed until the urine is clear of blood. As a rule no further treatment is needed, but for an occasional elderly patient dilations may be needed because of the sclerotic changes caused by advancing age.

Emmett<sup>62</sup> stated that obstruction of the urethra in infant boys usually is suspected because of the appearance of symptoms of urinary infection, such as fever, urgency and frequency of urination and painful urination as demonstrated by the infant's crying during micturition.

He reported a case in which a boy aged 18 months had urinary difficulties. Micturition was frequent and was accompanied by straining. This trouble had increased gradually in severity until, at the time of admission, the father said that the child "strained like an old man to urinate." At each micturition the child cried.

Cystoscopic examination was carried out with the infant under anesthesia produced by nitrogen monoxide. Only a moderate amount of urine was present in the bladder, some of which may have been residuary. The bladder, ureteral orifices and vesical neck appeared to be normal. On withdrawal of the cystoscope into the prostatic portion of the urethra an abnormally large verumontanum was encountered, which was of sufficient size to occlude the urethra almost completely. Careful examination of this structure failed to disclose any definite cystic formation. The hypertrophied verumontanum was fulgurated by means of an electrode through the cystoscope.

The results of fulguration were excellent. The patient was dismissed three days after fulguration, at which time he did not strain on voiding and the urinary stream was normal. He still cried during micturition, evidently because of irritation resulting from fulguration. Six weeks later he apparently had completely recovered, since he voided normally without discomfort and the urine was clear.

#### TESTIS

*Tumor*—Gilbert<sup>63</sup> summarized data concerning 126 small tumors of the testis. Of approximately 7,000 malignant tumors of the testis, only 126 (1.5 per cent) were situated in testes of normal or smaller than normal size. Of these, 118 were finally diagnosed accurately, although 11 were diagnosed only at necropsy.

The age of 113 patients averaged 32.3 years. In 48 cases the tumors affected the right testis, in 35 they affected the left testis, and in 2 they were bilateral (scrotal). Alleged trauma occurred in 15 cases (12 per

62 Emmett, J. L. Obstruction of the Vesical Neck of a Male Infant Produced by Hypertrophy of the Verumontanum. Report of Case, Proc. Staff Meet. Mayo Clin. 15: 364-365 (June 5) 1940.

63 Gilbert, J. B. Studies in Malignant Tumors of the Testis. I. Differential Diagnosis of Clinically Obscure Tumors. Four Cases and Review of One Hundred and Twenty-Two from the Literature. J. Urol. 43: 722-733 (May) 1940.

(cent) and appeared to be an important factor in the early removal of small tumors, even though the correct clinical diagnosis was not made.

There were 46 (36.5 per cent) unicellular and 71 (56.3 per cent) teratoid tumors (29 teratomas and 42 chorionepitheliomas).

Scrotal disease was evident on first examination in only 59 patients (17 per cent). Of these 59 patients, 32 were considered to have testicular tumors, whereas all other possible scrotal conditions were diagnosed in the cases of the remaining 27 patients. In 26 cases abdominal metastases were mistaken for intra-abdominal disorders, although only 16 of these were considered to be tumors. In the remaining 41 cases the patients were considered to have primary disease of the thorax, the head, the neck and even the extremities. Hormonal assays aided in formation of the correct diagnosis in 21 of 53 cases in which the patients were seen after 1932. Assays in which the results were positive also were made concerning 10 of 18 patients who had gynecomastia. In 2 instances repeated assays in which results were negative were consistent with clinical cures of respectively four and five years' duration.

Orchidectomy was performed on 67 patients, in 24 instances in the presence of metastases. Fifty-nine patients were considered to be inoperable. Five radical operations were performed. Irradiation therapy was applied to 40 patients, this number included 2 patients who received radium therapy.

Only 12 patients survived for five years or more (10 had unicellular tumors, and 2 had teratomas). Of the 10 patients who had seminomas, 2 died after periods varying between five and ten years, 8 patients were known to have survived.

Wesson<sup>64</sup> expressed doubt that tumors of the testicle are rare. Only those tumors have been reported which caused real trouble and brought the patients to urologists for treatment or caused them to apply for hospitalization, and because of this, only a few tumors have been reported. On the other hand, many men who have nonmetastasizing tumors live for the normal span of life and die of intercurrent infection, oblivious to the fact that they have been harboring an "inactive" cancer. Char, of the Peiping Union Medical College, wrote that in eighteen years he had seen 34 patients who had such tumors. The tumors were said to have been present for from six months to fifty years. Nineteen of them were of more than two years' duration.

Trauma usually is considered to be a probable predisposing factor in the causation of tumor, but Wesson believed that it is of no significance. At best, trauma is an eagerly remembered coincidence. A history of trauma always should be ignored unless the blow was adequate to produce some structural alteration visible to the naked eye, such as

<sup>64</sup> Wesson, M. B. Tumors of the Testicle. Report of Some Unusual Cases. *Tr. Am. A. Genito-Urin. Surgeons* 32: 347-358, 1939.

ecchymosis Ewing, after a very comprehensive investigation of the literature and careful study of many cases of tumors of the testicle which were alleged to have been traumatic in origin, concluded that data now at hand confirm the view, long since adopted by pathologists, that single traumatization of normal tissues is incapable of producing a malignant tumor His contention was that in a given case the growth was present and the trauma was merely a coincidence eagerly remembered by the patient

The presence of a teratoma is unknown to a patient afflicted with it until it becomes sufficiently large to manifest itself subjectively or objectively Frequently the pain or tumor is first noticed after slight strain or trauma, and, consequently, strain or trauma is assumed to be responsible for a condition that has long been present but has just progressed to active growth

Orchidectomy supplemented by ample high voltage roentgen therapy is the procedure of choice

Barringer,<sup>65</sup> in discussing Wesson's article on tumors of the testicle, stated that Ewing recently had given him the history of a patient whose entire course of life, from the time of appearance of the first symptom to death, was much shorter than the life of any of the patients in the cases reported by Wesson In Barringer's case the life of the patient was a matter of several weeks

The question of metastasis in these cases is very interesting Barringer had given, a year prior to the time of his discussion, expert testimony concerning the supposition that if a man had lived five years without metastasis he could be considered a fit candidate for life insurance During the next month he saw 2 patients who had been afflicted by metastasis five years after operation The condition of 1 patient was interesting He had had a teratoma of the testis treated originally at the Memorial Hospital in New York city, and he had lived for nearly six years thereafter without experiencing any symptoms Finally a tumor had developed to the left of the thyroid gland, accompanied by intense dyspnea The local surgeon wished to perform a tracheotomy, when the patient suddenly remembered that he had had a teratoma of the testis Barringer aspirated the supraclavicular mass, and Ewing, in about five minutes, gave Barringer the diagnosis of metastasis from the primary lesion Roentgenograms were made, and after about seven years (at the time of Barringer's discussion) the patient was still well This case shows the value of aspiration of a specimen of tissue for biopsy

Wesson apparently administered roentgen therapy after the operation on his patients Barringer thought it reasonable to administer roentgen treatment before operation on the testicle By virtue of moder-

65 Barringer, B S in discussion on papers of McKenzie Culver Wesson and Graves and Flo, *Tr Am A Genito Urin Surgeons* 32 386 1939

ate roentgen therapy to the testicle, he thought, several things could be accomplished. The testicle itself would have the benefits of preoperative roentgen therapy and would present the appearance of a good pathologic specimen, and the cells of the neoplasm, which are the most highly malignant cells recognized in any tumor occurring in the human body, would be devitalized before operation on the testicle.

Hagner<sup>66</sup> stated that he had only a moderate experience in the treatment of tumors of the testicle and that he had never believed that he could say much about them. The urologist sees some patients who have lived for years and others who die in a few months, and yet the pathologic reports may not be dissimilar. Hinman advised roentgen therapy after removal of the testicle, claiming that the surgeon cannot determine definitely the nature of cellular elements if the tumors have been submitted to preoperative roentgen therapy. Hagner, conversely, expressed the belief that roentgen therapy should be administered before the testicles are operated on.

In 1 of Hagner's cases a patient who had a seminoma, apparently of a rather malignant type, received roentgen therapy before the tumor was removed. The testicle was almost normal in size when it was taken out, it had regressed very much, and the patient made a good recovery. He remained perfectly well for nine years, then a tumor developed in his neck, and he came back to Hagner. By that time the Aschheim-Zondek test had been developed, the patient was tested, and the reaction was found to be positive. The patient received roentgen therapy, and the tumor literally "melted away" from his neck. Within a year, a tumor almost the size of an orange developed in the midline in his abdomen, evidently in the mediastinal glands. The reaction to the Aschheim-Zondek test had become negative after the tumor in the patient's neck had disappeared, and when he returned a year later with the tumor in his abdomen the reaction to the Aschheim-Zondek test was positive. That tumor was treated, and it disappeared. Although the reaction to the Aschheim-Zondek test became absolutely negative at that time, the patient had been apparently well for about a year and a half at the time of Hagner's remarks. This is an interesting case from the standpoint that the patient had lived for nine years, apparently well, before he had a recurrence of probably the same type of tumor that originally had appeared in the testicle.

Dean<sup>67</sup> stated that in Wesson's paper on testicular tumors Wesson had emphasized three points, namely, incidence, trauma as a causative agent and treatment.

<sup>66</sup> Hagner, F. R., in discussion on papers of McKenzie, Culver, Wesson and Graves and Flo, *Tr. Am. A. Genito-Urin. Surgeons* 32: 386-387, 1939.

<sup>67</sup> Dean, A. L., Jr., in discussion on papers of McKenzie, Culver, Wesson and Graves and Flo, *Tr. Am. A. Genito-Urin. Surgeons* 32: 389-390, 1939.

Concerning incidence, Dean said, at the Memorial Hospital in New York city teratomas of the testes comprise 3.4 per cent of all tumors of the genitourinary system, 2 per cent of all malignant tumors occurring in male patients and 1 per cent of all malignant tumors occurring in both sexes. These figures correspond roughly to a frequency of from 1 to 3 per cent of all malignant tumors found by other investigators.

In Dean's experience, teratomas have been seen nearly twice as frequently as cancers of the penis. That these figures may vary widely in different institutions is shown by the fact that Char, of Peking, China, said that in a year he operated on 200 patients with penile cancer, whereas at the Memorial Hospital only about 20 new instances of penile cancer are encountered within the same length of time.

Dean considered trauma to be a causative factor in the production of such tumors. If it is true that teratomas arise from misplaced sex cells, it would be difficult to attribute much importance to trauma as a causative agent, but, on the other hand, Wesson has not exaggerated the medicolegal importance of this problem, since in medicolegal cases trauma is usually alleged to be a factor. However, tumors are discovered so frequently after an injury to the testes has occurred that any possible relation between trauma and the development of these tumors should be studied. Tissue in testicular tumor is denser and heavier than normal testicular tissue. Dean expressed the belief that the added weight of the tumor causes the testis to hang lower and prevents the normal reflexes, which ordinarily lift the testis to protect it from threatened injury, from functioning so efficiently as these reflexes would act if no tumor were present. Thus, a testis which is the seat of tumor is more likely to be traumatized than is a normal testis. The injury draws the attention of the patient to the testis, and, in turn, a tumor is discovered by the physician. It is sometimes very difficult to explain to a jury why an injury cannot hasten the dissemination of a tumor admittedly present at the time of injury.

In most clinics, irradiation is of recognized value in the treatment of testicular teratomas, but there are still differences of opinion as to the best procedure to employ. Hinman is said to remove the testis without preoperative therapy, so that he may study its structure and make hormonal assays. Dean said that preoperative irradiation offers advantages because five year end results show a rate of survival 35.7 per cent greater for patients who have received roentgen therapy before undergoing orchidectomy than for patients who have been operated on first and have then received roentgen therapy as soon as the diagnosis has been made. In neither group were metastases demonstrable at the time of operation.

Interpretation of the results of histologic examination of a tumor after irradiation is largely a question of the training of the pathologist.

There are so-called ghost cells which are recognizable as devitalized tumor cells

There seems to be agreement concerning the question of irradiation of the lymphatic pathway through the pelvis and abdomen to the epigastrium in all cases, whether or not metastases can be found. When this treatment is administered, the anterior and posterior portals are treated with fractionated doses carried to as high a total dose as possible. In this way a single cycle may be sufficient.

Of all Dean's patients who had teratoma (there were between 500 and 600 with teratoma of the testis), 29 per cent were without evidence of disease at the end of five years. Seventy-two per cent had had metastasis at the time of treatment. Considering only a smaller group, members of which were considered to be "primary operable" patients who had testicular tumors without evidence of metastases, the five year survival rate for the group was 78 per cent.

#### PENIS

*Priapism*—Dawson<sup>68</sup> reported 5 cases of true priapism. Four patients recovered after treatment by multiple aspiration of the corpora cavernosa. Two of the 4 had sickle cell anemia. Sickle cell anemia has not been reported heretofore as associated with priapism. The part this associated factor plays in priapism is not known or discussed. The fifth patient died after the penis became gangrenous and was amputated and after urinary extravasation had occurred. Dawson noted that heat as a local agent is better than cold.

#### URETHRA

*Calculi*—Culver<sup>69</sup> discussed primary posterior urethral calculi. The old literature abounds with reports of urethral calculi, and the majority of such reports deal with calculi of the anterior segments of the urethra. Englisch, reviewing 405 cases of impacted urethral calculi without regard to primary or secondary types, found that 58 per cent of the calculi were situated in the anterior portion of the urethra and 42 per cent in the posterior segment. In approximately one third of all recorded cases of posterior urethral calculi the stones are multiple, varying in number, size and contour according to their chemical content and the space within which they are confined.

68 Dawson, G. R., Jr. Priapism. Report of Five Cases, Two Cases Occurring with Sickle Cell Anemia, *J. Urol.* **42**: 821-828 (Nov.) 1939.

69 Culver, H. Primary Posterior Urethral Calculi, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 337-346, 1939.

All the 7 patients reported on by Culver, who ranged in age from 16 to 65 years, had definite prostatic bars and long-standing histories of urinary disorders, caused in the beginning by bars of either the congenital or the acquired type. The topography of the posterior part of the urethra in the presence of a bar facilitates retention of urine between the bar and the external urethral sphincter. If the constitutional factors necessary to the formation of stone are also present, the picture would seem to be complete for the beginning and progression of these calculi.

Establishment of the diagnosis of urethral calculi is usually definite and complete when the long-standing history is considered and when posterior urethral obstruction is encountered with a metal instrument. In most patients the instrument cannot be passed into the bladder, but the diagnostic metallic click which is heard is sufficient. Rectal examination likewise reveals observations absolutely diagnostic. The rounded, hard midline projection, sometimes fixed, sometimes movable, with crepitus, associated with multiple stones should not be difficult of correct interpretation.

Roentgen examination confirms the diagnosis with adult persons, but may be of no value with children, in whom uric acid or urates may be the only constituent of the stones. Roentgenograms should be made from both the anteroposterior and the semilateral position to determine the size, extent and number of the calculi present. Urethrograms contribute to the diagnosis because they permit visualization of complications, such as diverticula of the urethra or of the bladder.

Calculi in this situation, if they were small enough, possibly could be removed with forceps, and such a procedure frequently is used when secondary stones are present and the patient has had recent acute symptoms, but removal of stones of the primary type which have caused long-standing symptoms should not be attempted by this method.

The perineal approach, in which Young's prostatectomy exposure is utilized, has been used, but it has the technical difficulty of revision of the vesical neck, which is an important feature of a complete operation, it likewise requires for traction a urethra patent in the prostatic region, a condition which is not frequently present.

The suprapubic approach has been ideal for all patients in Culver's experience because it allows bimanual extrusion of the stone into the bladder, which is done by insertion of the surgeon's finger into the patient's rectum. Even with this help from below, the surgeon occasionally is forced to cut the vesical neck to accomplish his purpose. After the stone has been removed, it is a simple procedure, under vision, to remove the obstructing tissue of the vesical neck with either an electric loop or a suprapubic cold punch.

Postoperative management of the patient obviously consists of dilation of the posterior part of the urethra and careful attention to the prevention of infection of the urinary and genital tracts. Attention to distant foci of infection as well as to dietary and medicinal management for the purpose of preventing recurrence has its place in the treatment of patients with this type of stone, just as it has a place in the management of patients with any other type of urinary calculus.

*Urethritis*—Spence<sup>70</sup> discussed a series of cases in which granular urethritis was present in women. In approximately one third of the cases a considerable degree of pyuria may be expected to be present. He expressed the belief that granular urethritis often will be found to be the cause of cystitis. If instances of bullous edema of the trigon, trabeculation and cystitis cystica were excluded, it would be found that cystoscopic examination disclosed acute or subacute cystitis to be present in 25 per cent of Spence's cases.

Gross hematuria, usually in the form of small clots appearing toward the end of micturition, was present in 9.5 per cent of the cases and justifies the inclusion of granular urethritis in a prominent position in the list of causes of blood in the urine of the female patient.

Polypoid and cystic masses were found in the unexpectedly high portion of 61 per cent of Spence's cases. It was Spence's impression that this figure, which is much higher than that usually given, is the result in part of his consistent use of foroblique instruments for scrutinizing the entire urethra, a procedure which enables him to detect many lesions which were overlooked previously, when he used right angle lenses.

Extensive light fulguration of the entire urethral lining has yielded more permanent symptomatic results and more instances of satisfactory late visual appearance of the urethra than were possible before.

Disturbances of the female urethra occurring during childhood parallel exactly similar disturbances in adult patients. The management of the patient is similar.

*Stricture*—Alken and Zumach<sup>71</sup> are of the opinion that a preliminary urethrogram should be made in all cases of urethral stricture before clinical treatment is carried out. In the average case Alken and Zumach's treatment of the patient is similar to the treatment used in the United States, in that they use increasingly enlarged catheters at

<sup>70</sup> Spence, H. M. Granular Urethritis in Women, *J. Urol.* **43**: 199-203 (Jan.) 1940.

<sup>71</sup> Alken, C. E., and Zumach, E. Die klinische Behandlung der Harnstricture. *Ztschr. f. Urol.* **33**: 498-510, 1939.



sounds for dilation. They still perform internal urethrotomy for severe contractures, but they do internal urethrotomy only after they have performed suprapubic cystostomy.

#### SCROTUM

*Carcinoma*—In discussing the treatment of carcinoma of the scrotum, Graves and Flo<sup>72</sup> stated that irradiation should not be relied on for the destruction of this tumor. The metastatic process in the groin seems stubbornly resistant to roentgen therapy, and the thin scrotal wall, which is almost lacking in normal tissue defenses beneath the primary growth, offers a poor field for the use of either radium or roentgen rays.

Basing their surgical methods solely on anatomic considerations, the authors wrote that it might be necessary to advocate complete removal of the entire scrotum, together with the skin of the base of the penis and the nodes of the groins en bloc, because this is a lymph-borne disease and because, as has been shown, there is an unusually free communication among the lymphatic vessels of this region. Fortunately, pathologic and clinical evidence suggests that less drastic procedures may be safe. The lymphatic-embolic mode of dissemination of this particular type of cancer renders it futile, probably, for the surgeon to attempt to remove the intervening channels between the tumor and the glands, and further support of this view is found in the fact that Graves and Flo have seen no instance of local recurrence of this tumor in the scrotum after adequate local excision has been performed, even in their series in which there was eventually a high mortality rate. The involved portion of the scrotum must be excised completely, together with a wide margin of surrounding normal scrotal wall. Undoubtedly, some degree of direct permeation occurs along lymphatic vessels in the immediate vicinity of the tumor. When the lesion lies near the median line, dissection should extend well on the opposite side, for the raphe has no significance so far as the lymphatic vessels are concerned, and the pathways of these vessels are continuous from one side to the other. Electrosurgical handling is desirable in these operations on the scrotum, because it aids in the control of hemorrhage.

Graves and Flo wrote that they sacrifice the testicle and divide the spermatic cord well above the external inguinal ring, at least on the side affected by the tumor. There is no lymphatic communication between the scrotum and the testis or its tunica, but closure of the remaining portion of the scrotum will be difficult in most cases if both gonads are spared and if more extensive excision is performed may be impossible unless both gonads are removed.

<sup>72</sup> Graves, R. C., and Flo, S. Carcinoma of the Scrotum, *J Urol* **43** 309-332 (Feb.) 1940.

Both groins must be dissected. On the side on which the tumor is situated the incision that surrounds the neoplasm may be continued upward and outward, a little above and parallel to Poupart's ligament, to within 2 cm of the anterior superior spine of the ilium. Then it should curve widely downward and inward across the lowest level of the femoral triangle. By turning medially the resulting broad-based flap of skin, the surgeon may gain ready access to the inguinal and femoral regions, so that all of the gland-bearing tissues may be removed en bloc, with the tumor, testis and cord. Another plan that may be used continues the scrotal incision upward and outward only until the incision communicates with an incision in the groin which curves in the other direction, beginning near the anterior superior spine, extending above Poupart's ligament to the spine of the pubis and then curving widely downward and outward across the lower portion of the femoral region. The flap is dissected laterally so that access to the gland-bearing region can be secured. In dissection of the groin in recent years Graves and Flo have employed these curved incisions in an effort to avoid as much as possible the sharp corners and acute angles which have seemed in the past to invite necrosis.

Every radical dissection of the groin in cases of scrotal cancer must be carried out with meticulous attention to the anatomic aspects of the lymphatic vessels as described previously.

#### HYDROCELE

Young<sup>73</sup> stated that the nonoperative treatment of hydrocele is often unsatisfactory. Simple aspiration is followed by early recurrence of the fluid and sometimes by infection.

The injection treatment often fails to cure the hydrocele and frequently results in the formation of painful adhesions.

Complete excision of the sac has encountered the objection that many blood vessels which require ligation may be found, and after ligation has been done postoperative extravasation of blood may occur. The bottle operation with inversion of the sac, a procedure introduced to avoid these operative difficulties, is not infrequently unsuccessful and leaves a large mass situated back of the testicle and epididymis.

A new operation has been devised by Young which provides for incision of the sac layer by layer and stripping of the layers back until thin serous membrane is reached, this alone is excised. In this way hemostasis is easily secured, since few vessels remain to be ligated. The operation is thus made more nearly accurate and less destructive and hemorrhagic than other procedures, and it is radically curative.

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73 Young, H. H. Radical Cure of Hydrocele by Excision of Serous Layer of Sac, Surg., Gynec. & Obst. 70 807-812 (April) 1940.

## GLANDULAR THERAPY

Heckel<sup>74</sup> reported that testosterone propionate injected daily into muscle produced little improvement in the symptoms and clinical course of 22 patients who had benign prostatic hypertrophy. It did not produce any noteworthy reduction in the amount of residual urine. Histologic examination of tissue from the prostate glands of patients who previously had been treated with testosterone propionate disclosed no variation from the appearance of sections from untreated patients. Testosterone propionate produces a temporary depletion of spermatozoa in patients who have spermatozoa in normal numbers. In 10 of 12 patients oligospermia was produced. These data would indicate that this material is of little benefit in the treatment of benign prostatic hypertrophy, and its promiscuous use for a long period for patients who have normal testicular function might be harmful.

Korenchevsky and Ross<sup>75</sup> have noted in previous publications that the weight of the kidney in rats was decreased after castration and increased after injection of androgens. They noted also that there was an apparent decrease in the size of the kidneys after ovariectomy. Simultaneous injection of both androgens and estrogens produced hypertrophy of the kidneys. Their latest investigation was made to correlate and confirm the previous observations.

The total number of normal rats investigated was 148, of which 70 males and 12 females were kept as controls and 31 males and 35 females were given injections. The total number of gonadectomized rats was 418, of which 59 males and 21 females were controls, 142 males and 39 females were given injections of androgens, 20 males and 34 females were given injections of estrone, estradiol or esters of the latter, and 48 males and 55 females were given simultaneous injections of both androgenic and estrogenic substances.

The experiments were carried out on 178 rats for twenty-one days and on the remaining 388 rats for two to three and three-quarters months.

In agreement with the absence of any definite change in weight of the kidneys, no significant change in the size of the tubules, either by weight or histologically, was found in ovariectomized rats. In castrated rats the measurements showed a definite decrease in the size of the convoluted tubules. Thus, the definite decrease in the size of the kidneys

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74 Heckel, N. J. The Influence of Testosterone-Propionate upon Benign Prostatic Hypertrophy and Spermatogenesis. A Clinical and Pathologic Study in the Human, *Tr Am A Genito-Urin Surgeons* **32** 237-261, 1939, *J Urol* **43** 286-308 (Feb) 1940.

75 Korenchevsky, V., and Ross, M. A. Kidneys and Sex Hormones, *Brit M J* **1** 645-648 (April 20) 1940.

after castration can be explained by slight atrophy of the tubular secretory apparatus in these organs

In both normal and gonadectomized female rats and castrated male rats, the androgenic substances, androsterone and esters of testosterone, produced true hypertrophy of the kidneys and could therefore be defined as nephrotrophic substances

The action of testosterone esters on the kidneys appears to be definitely beneficial. On the other hand, when estrogens were injected into the animals for prolonged periods, there was no increase in the weight of the kidneys or in the size of the tubules, but there was cystic degeneration of the tubules in the boundary layer of the cortex and medulla, with atrophy of the tubular epithelium and marked peritubular edema

When the androgens and estrogens were injected simultaneously into the rats, the hypertrophizing effect of the androgens remained the same. The pathologic effects of the estrogens (dilatation of the tubules, formation of small cysts and development of peritubular edema and hyperemia) were prevented or decreased by the neutralizing effect of the androgens in some rats only. Some animals were as well developed as animals that had received injections of estrogens alone

Since androsterone has only a weak action on the female sex organs and occurs normally in the female organism, this substance might also be cautiously tested in suitable renal diseases of women

In women suffering from these diseases, however, the administration of estrogens, especially in large doses or for prolonged periods, probably would increase the pathologic changes in the kidneys

Merk<sup>76</sup> tried treatment with testosterone propionate in a series of cases of prostatic enlargement. No success was obtained in 10 cases in which large prostatic adenomas and large amounts of residual urine were present. In 32 instances of early enlargement in which less than 100 cc of residual urine was present, symptoms of prostatism disappeared after twelve injections of 10 mg of the substance. Most of the patients said that they felt much better after the treatment

In 20 cases in which it was necessary to do some kind of operation, the general condition of the patients was considerably improved by injections. Merk discontinued the glandular treatment one week before operation and did not continue it after operation, since he was of the opinion that severe hemorrhage may develop as a result of hyperemia caused by the glandular substances

<sup>76</sup> Merk, K. Ueber die Verwendung synthetischen Testishormons in der konservativen und chirurgischen Therapie der Prostata-Hypertrophie, *Ztschr f U*, 33 573-577, 1939

## VITAMIN THERAPY IN UROLOGY

Wildbolz <sup>77</sup> carried out systematic investigations of the ascorbic acid metabolism of patients who had various urologic and surgical lesions. He found that such patients rarely suffered from hypovitaminotic conditions. There was no regular parallelism between recovery or therapy and vitamin C content, and he was unable to reduce the number of postoperative complications by therapy with vitamin C.

## HEMATURIA

McKenna and Birch <sup>78</sup> stated that there is a group of cases in which hematuria is present, either alone or accompanied with other hemorrhagic phenomena, and in which there is no demonstrable pathologic condition of the urogenital tract. The causative factor is a pathologic condition of the elements of the blood or of the capillaries. The most important conditions are the purpuras, essential or symptomatic, hemophilia and avitaminosis C. Not infrequently hemorrhage from the kidney is the most prominent symptom, and occasionally it may be the only symptom, so that the patient is referred to the urologist. It is essential that such conditions as these be recognized and evaluated, because urologic manipulation or surgical treatment will do the patient no good whatever and may be definitely harmful. Every patient who has hematuria of unknown causation should have the benefit of complete studies of the blood and also of determinations of the ascorbic acid content of the blood.

## CARCINOGENIC AGENTS

Caldwell <sup>79</sup> stated that various hydrocarbons, derived from coal tar or synthetically prepared, will produce cancers in experimental animals of different species. The tumors produced are either carcinomas or sarcomas, depending chiefly on the application of the active agent to the epithelium of the surface of the skin or the introduction of the agent into the deeper tissues. The latent period preceding the appearance of the tumor is relatively long, and its length seems to have some relation to the life span of the particular species of animal used.

The estrogens, administered in huge doses, are undoubtedly carcinogenic, and in susceptible strains of animals even physiologic concentrations seem to determine largely what the incidence of tumors will

77 Wildbolz, E. Systematische Untersuchungen über die Rolle des Vitamins C in der Chirurgie und Urologie, *Ztschr f Vitaminforsch* 9 223-238, 1939

78 McKenna, C. M., and Birch, C. L. Hematogenous Hematuria, *J Urol* 42 171-182 (Aug) 1939

79 Caldwell, G. T. Chemical Carcinogenic Agents, *J Urol* 42 651-673 (Nov) 1939

be in those organs which are subject to repeated stimulation by means of these substances

Many tumors produced by chemical agents in one animal have been transplanted into other animals of the same species, and some have been transferred in this way through many generations. Apparently, stimulation by the original carcinogenic agent is no longer necessary for the subsequent growth of the tumor. The cells which constitute the tumor seem to have acquired new characteristics, and these characteristics, whatever they may ultimately prove to be, are transmitted without fail to all tumors which stem from the original tumor by the experimental process of transference.

#### UROLITHIASIS

Flocks<sup>80</sup> stated that the level of urinary calcium is a very important link between calcium metabolism and the development of calcium urolithiasis.

The excretion of calcium in the urine of the normal person and in that of the person who is undergoing certain intrinsic changes in his body mechanisms is discussed. More specifically, the effects on the urinary calcium of bodily immobilization, intrinsic osseous disease, certain endocrine changes, certain intrinsic renal changes and certain intrinsic variations the mechanism of which is not as yet understood are described. The possibility of increasing and decreasing the excretion of calcium in the urine under these several conditions by means of changes in the patient's calcium and phosphorus intake, acidity of the ash of the diet and vitamin D intake is discussed.

The management, from the point of view of calcium metabolism, of the patient who has calcium urolithiasis is discussed under three headings: (1) the prophylaxis of urolithiasis for patients who have conditions in which the urine has a high content of calcium, (2) the management of patients who have calcium urolithiasis and in whose urine the content of calcium is high, and (3) the management of patients who have calcium urolithiasis and whose urine has a normal or a low content of calcium.

Eisele<sup>81</sup> analyzed the records of all patients from the University of Chicago Clinics between 1927 and 1939 who had ureteral or renal calculi. He did this with the object of determining the relation between the treatment of peptic ulcers and the formation of urinary stones.

<sup>80</sup> Flocks, R. H. Calcium Urolithiasis. The Rôle of Calcium Metabolism in the Pathogenesis and Treatment of Calcium Urolithiasis, *J. Urol.* **43** 214-233 (Jan.) 1940.

<sup>81</sup> Eisele, C. W. Role of Alkali Therapy for Peptic Ulcer in Formation of Urinary Calculi, *J. A. M. A.* **114** 2363-2366 (June 15) 1940.

Conditions favorable to formation of stone are produced by the usual medical treatment of ulcer, namely, increase in urinary solids, high specific gravity, excretion of large amounts of crystalloids and a shift of the  $p_H$  of the urine to the alkaline side. Theoretically, hyperexcretory calculosis should be common among patients who are under treatment for ulcers.

Eisele found that, among 505 patients who had renal or ureteral calculi, 43, or 8.5 per cent, had peptic ulcers of which the symptoms antedated the symptoms referable to stone, and all of the patients had received the Sippy type of treatment. In addition, 13 patients, or 2.6 per cent, had chronic gastrointestinal distress and habitually took large amounts of alkalis for relief. Thus, there were 56 patients, or 11.1 per cent, among those who had lithiasis, in whom the ingestion of alkalis may have played a role in the formation of urinary stones.

The hyperexcretory calculosis which developed in these patients demonstrates the potential danger of alkali therapy for patients who have peptic ulcers.

#### CHANCROID

Schwartz and Freeman<sup>82</sup> discussed sulfanilamide in the treatment of chancroid and reported a series of 37 cases. For comparison there was also presented, as a control group, a series of 60 similar cases in which the patients were treated by other methods.

Various doses administered daily were used and evaluated. The average dose for the total group was 46 grains (3 Gm.) of sulfanilamide a day. The total dose varied between 280 and 950 grains (18 and 62 Gm.) and averaged 642 grains (42 Gm.) per patient. After the initial dose of from 3 to 4 Gm., the maintenance dose was determined by the clinical response and by the weight and age of the patient. A high maintenance dose is of the utmost importance. The least desirable combination is a low initial dose and a low maintenance dose. The next least desirable is a high initial dose and a low maintenance dose. The combination of a low initial dose and a high maintenance dose is more desirable, whereas the combination of a high initial dose and a high maintenance dose is the most desirable.

Including all the various types of lesions, the average period required for healing in the control group was slightly more than thirty-two days. In comparison, for the patients treated with sulfanilamide this time varied from seven to twenty-three days and averaged fifteen and seven-tenths days. Chancroidal ulcers situated elsewhere than on the glans penis responded best to treatment. Chancroidal bubo, unruptured, was next most responsive. There was little difference in the response

<sup>82</sup> Schwartz, W. F., and Freeman, H. E. Sulfanilamide in the Treatment of Chancroid. *J. A. M. A.* **114**: 946-947 (March 16) 1940.

to sulfanilamide of ruptured, chancroidal bubo, and the response of ulceration of the glans penis, but the latter lesion was slightly less responsive

#### ENURESIS

Sitkéry<sup>83</sup> reported a series of 196 cases of enuresis in which he had done manometric examinations of the bladder. He concluded that the underlying pathologic process is an increased irritability in the afferent nerve fibers of the bladder. This irritability causes pollakiuria, which Sitkéry stated is identical to, and always associated with, enuresis. He therefore preferred to call this condition "pollakiuria enuretica."

#### URINARY ANTISEPTICS

Weyeneth<sup>84</sup> reviewed the literature on mandelic acid and presented the results of treatment of urinary infections obtained in the Geneva Medical Clinic with the new compound amanol. Amanol, which contains mandelic acid, combines in a 1 Gm tablet the following substances: methenamine phenylglycolicum, 0.2 Gm; calcium phenylglycolate, 0.7 Gm; sulfanilamide (paraaminobenzenesulfonamide), 0.1 Gm. In the treatment of advanced types of urinary infection, including that caused by *Bacillus coli*, and also in the treatment of mixed infections the results have been uniformly good. In cases of complicated urinary infections aggravated by stones and tumors, the results naturally were not so satisfactory. It is necessary, as in the treatment with simple mandelic acid, that the intake of fluids be restricted. Weyeneth stated that the main advantages of amanol over other mandelic compounds is that it is well tolerated by the stomach.

Buchtel and Cook<sup>85</sup> reported the results of neoarsphenamine therapy for infection of the urinary tracts of 258 patients, 149 males and 109 females ranging in age from 10 to 77 years. Diagnostically, especially in the presence of coccic infections, Gram's stain of the centrifuged urinary sediment is more valuable even than special culture mediums. The presence of either bacteria or pus in the urine is good evidence that disease exists in the upper part of the urinary tract and not in the prostatic region.

The criteria for cure of bacillary infection in men were absence of bacteria and pus in the urine and sterile prostatic cultures. For women these criteria were absence of bacteria and pus in the urine and absolute

<sup>83</sup> Sitkéry, J. Untersuchungen über die Pathologie der sogenannten Enuresis nocturna, *Ztschr f Urol* **33** 409-421, 1939.

<sup>84</sup> Weyeneth, R. Die Mandelsäure in der Bekämpfung der Harnwegsinfektionen unter kritischer Berücksichtigung eines zweckmässig kombinierten Therapeutikums, *Schweiz med Wchnschr* **69** 1297-1302 (Dec 23) 1939.

<sup>85</sup> Buchtel, H. A., and Cook, E. N. Neoarsphenamine in the Treatment of Urinary Infections, *J Urol* **43** 417-426 (Feb) 1940.



relief of symptoms. Final certainty of cure was assumed if no recurrence was noted during the first three months after cessation of treatment.

Bacillary infection responded very poorly to neoarsphenamine therapy, as did nonspecific prostatitis. Infection caused by *Streptococcus faecalis* responded to acidification therapy alone or in combination with neoarsphenamine. Instances of so-called amicrobic pyuria, in which bacteria could not be demonstrated in the urine even after special efforts, did not respond. However, if bacteria were demonstrated, results were satisfactory. Response to treatment was better in cases in which the upper part of the urinary tract was involved than in those in which the bladder was involved. These results were especially favorable in cases of uncomplicated infection.

Improvement usually appeared after the first injection of neoarsphenamine. Increasing doses should be used in subsequent injections in cases in which there has been no response. Only two doses should be administered in cases in which no improvement is demonstrated. Results were better when they were accompanied by urinary acidification. Four doses are all that are usually indicated.

Of the 189 patients who had coccal infections and who were treated with neoarsphenamine, 17 per cent had reactions, which is a higher proportion of reactions (and the reactions were of a more severe type) than is the case when neoarsphenamine is used specifically.

#### UROGRAPHY

Braasch and Doss,<sup>86</sup> in discussing the clinical value of the delayed urogram, said that the difficulty in determination of the cause of stasis visualized in the delayed urogram often diminishes its clinical value. It is possible that more precise methods of determining the ureteropelvic physiologic picture than have been employed in the past may aid in this respect. However, the delayed urogram is often of definite value in determining ureteropelvic obstruction, particularly in "borderline" cases. Unless the existence of stasis can be visualized in these cases, surgical intervention usually is not indicated. The delayed urogram also may be of value in the identification of doubtful roentgen shadows in the ureter or kidneys. In spite of the fact that the observations are sometimes puzzling, the method deserves more frequent employment.

#### RETROPERITONEAL TUMORS

Kretschmer<sup>87</sup> reported a case of retroperitoneal lipofibrosarcoma in which the patient was a child.

<sup>86</sup> Braasch, W. F., and Doss, A. K. The Clinical Value of the Delayed Urogram, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 119-125, 1939.

<sup>87</sup> Kretschmer, H. L. Retroperitoneal Lipofibrosarcoma in a Child, *Tr. Am. A. Genito-Urin. Surgeons* **32**: 57-71, 1939.

It is generally noted that the age of patients in whom retroperitoneal lipoma occurs with greatest frequency is from 40 to 60 years. In the series of 42 cases studied by Pemberton and McCaughan, the youngest patient was 28 years old, the oldest was 68 years old, and the average age was 49.3 years.

This tumor may reach enormous proportions. One of the largest tumors was that described by Hirsch and Wells, which weighed 69 pounds (31.3 Kg.). From the standpoint of clinical pathology, retroperitoneal lipomas present two very interesting aspects: (1) recurrence is relatively frequent with growths that are histologically benign and (2) in certain cases a recurrent tumor which originally had been histologically benign shows malignant changes.

Concerning the point of origin, it may be said that this frequently is hard to determine, except for the fact that it is known that the tumor arises in the retroperitoneal space. When the tumor comes to clinical observation and operation, it has, in the average case, reached huge dimensions and fills much of the retroperitoneal space. There is a general tendency for urologists to regard all such tumors as simply retroperitoneal rather than to try to distinguish those arising from the root of the mesentery or those which are perirenal in origin. Mayo and Dixon found that 80 per cent of simple retroperitoneal lipomas arose in the abdomen and that 20 per cent arose in the pelvic region.

As a result of the growth of the retroperitoneal lipoma, secondary changes may occur in the urinary tract which may lead to complete destruction of the kidney. Displacement and compression of the ureter may result in hydronephrosis. A large retroperitoneal lipoma may envelop the kidney so that pressure atrophy results, or the kidney may show more or less dilatation caused by obstruction at the ureteropelvic junction or below that point. Not infrequently a retroperitoneal fatty tumor surrounds the kidney and its pelvic structures so completely that removal of the mass necessitates nephrectomy. This operation was done in 50 per cent of the reported cases.

In the majority of reported cases the tumor had caused no symptoms until it reached such a size that abdominal swelling was noted or until it produced pressure symptoms on various organs (usually the digestive or the genitourinary tract).

Radical extirpation is the only possible treatment of retroperitoneal lipomatous tumors. Since in most cases symptoms are absent until the growth has attained a huge size, the operation is necessarily very difficult, considering the adhesions frequently encountered and the close proximity of the growth to important structures and to large blood vessels. In the case reported by Kretschmer the operation was easily carried out. The entire tumor was shelled out as easily as any lipoma could be shelled out except that adhesions were present at the upper pole, where the tumor was firmly attached to the muscles of the back.

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removal of the tumor and surrounding bowel. Three of these were in the sigmoid flexure of the colon and 1 in the rectum. The flat soft tumor in the ampulla of the rectum was in a perfectly healthy man whose only symptom had been bleeding. The biopsy was inconclusive, but because of one small area of induration a radical removal of the section



Fig 17—Drawing of a resected rectum containing a small carcinomatous ulcer on an adenoma, a flat adenoma and a small nodule of hyperplasia the latter shown in figure 1

was carried out. The pictures of the gross lesion, the results of biopsy and the sections taken through the area of induration accompany the text and bear out the wisdom of radical removal of polypoid tumors of the bowel when only a suspicion of their malignancy exists because of induration in a part of the tumor (figs 20 21 and 22)